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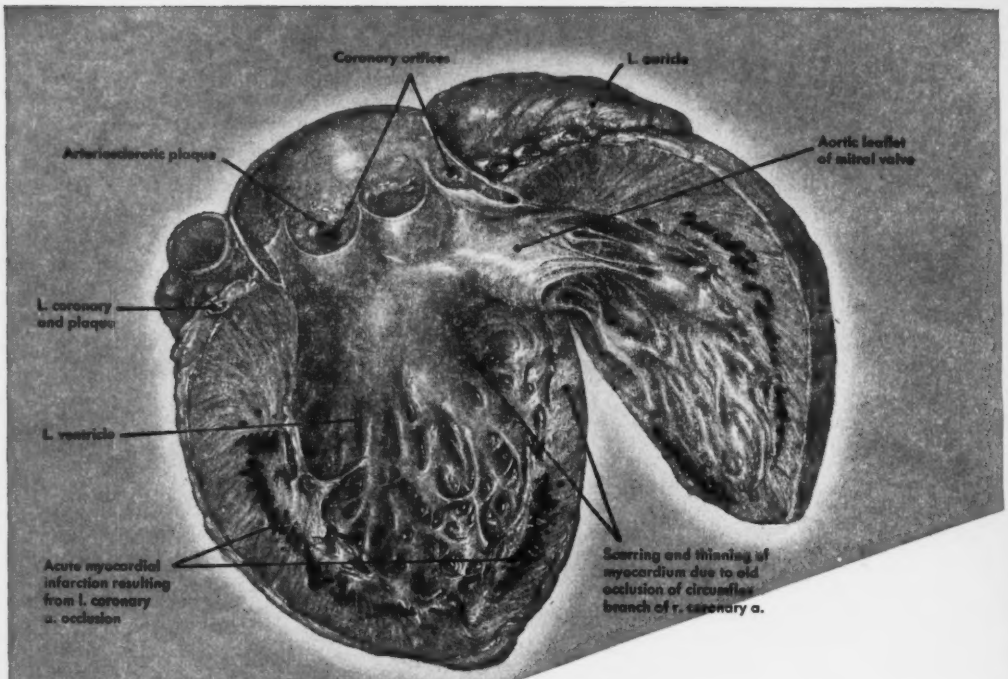

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Congenital Mitral Stenosis

By CHARLOTTE FERENCZ, M.D., ARNOLD L. JOHNSON, M.D., AND F. W. WIGLESWORTH, M.D.

Nine cases of congenital mitral stenosis are presented, with a review of 34 cases from the literature. A high incidence of associated malformations of the aortic valve, the aorta and the ductus arteriosus is apparent. Clinical findings and results of investigative procedures have been reviewed. Mitral stenosis is responsible for severe circulatory alterations and the development of hypertensive pulmonary vascular changes. This malformation has serious consequences. It is associated with early mortality and renders ineffective the surgical repair of associated coarctation of the aorta or patent ductus arteriosus.

CONGENITAL mitral stenosis has hitherto been considered a rare lesion and only of academic interest, but our attention has recently been directed to the frequent occurrence and practical importance of this malformation. The presence of mitral stenosis in association with other cardiovascular malformations may, on the one hand, alter the hemodynamic sequelae of these associated lesions and, on the other, render their successful surgical correction of no avail. The diagnosis of mitral stenosis in infancy is difficult, and this difficulty is enhanced by the usual association of other abnormalities of the heart or the great vessels.

The present report is based upon a study of nine cases of congenital mitral stenosis encountered in The Children's Memorial Hospital since 1939 and upon a survey of 34 cases reported in the literature since 1846. In all instances, a significant degree of anatomic stenosis of the mitral valve and a functioning left ventricle were present. Cases of rudimentary mitral valve ("atresia") and nonfunctioning left ventricle have not been included. It will also be noted that there are no cases of Lutembacher's syndrome in this series. Mitral stenosis, as an isolated malformation, occurred infrequently and was usually associated with lesions involving the aortic valve and the aorta and only rarely with intracardiac defects (table 1).

In view of the variety of defects associated with the mitral stenosis in our nine cases, it is not feasible to discuss their clinical picture as a group, and it will be necessary to outline briefly the findings in each patient. However, certain observations may be of help in the approach to this difficult diagnostic problem; reference is made to table 2. This group of infants was underweight. Three of them (cases 1, 5, 9) were without symptoms until the age of 9, 8, and 3 months, respectively, when symptoms of acute respiratory distress occurred. Six were in congestive heart failure at some time during the period of observation. The occurrence of pulmonary edema has been given careful consideration. This was an important feature in the clinical course of case 1, and cases 5, 6, 7 and 9 suffered from episodes of respiratory distress which may have represented pulmonary edema. Auscultation was not helpful, for, in only one instance (case 1) was a mitral diastolic murmur heard, and it was transient. In this patient, however, the mitral first and the pulmonic second sounds were abnormally accentuated. The observa-

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TABLE 1.—*Incidence of Malformations Associated with Congenital Mitral Stenosis*

Associated malformation	C.M. Hosp. 9 cases	Literature 34 cases	Total 43 cases
None	—	8	8
Patent ductus	5	12	17
Aortic stenosis	4	8	12
Patent foramen ovale	1	7	8
Coarctation of aorta	3	4	7
Aortic valve abnormality	—	5	5
Hypoplastic aorta	—	2	2
Tricuspid valve abnormality	—	2	2
Pulmonary valve abnormality	—	1	1
Defect of ventricular septum	1	1	2
Double aortic arch	1	—	1
Fibroelastosis*	8	17	25

* In our own cases we have considered it more likely that the fibroelastosis is a stress effect than a congenital lesion.

tions regarding the sounds were, in many cases, not sufficiently well described to be assessed.

The electrocardiogram in the five patients in which it was recorded, showed a pattern of right ventricular hypertrophy, even though, in three of these, the mitral stenosis was associated with lesions which placed a strain on the left ventricle. The evaluation of P-wave changes was confusing, since, in the two cases (1 and 8) in which the P wave was abnormal, it was tall and pointed and interpreted as indicating an increase in the right atrial mass.

The degree of cardiac enlargement observed radiologically was variable. Four patients had extremely large hearts, but, in case 1, a patient in whom there were episodes of pulmonary edema, the heart was only slightly enlarged. Fluoroscopic examination, which was done in three patients (cases 1, 5, 6), revealed no esophageal deviation suggestive of left atrial enlargement.

One patient was studied by cardiac catheterization (case 1). The catheter passed through the ductus arteriosus into the descending aorta and the pressures in the two great vessels were similar. Unfortunately, the pulmonary "capillary" pressure was not recorded.

An angiocardiogram was obtained in case 5 and the presence of mitral stenosis was inferred by the delay in the emptying of the enlarged left atrium.

CASE HISTORIES

Case 1. J. H., a 26 month old male child, did well until the age of 9 months when his appetite was observed to fail. At 1 year of age he had the first of three attacks characterized by cough and orthopnea. Between the ages of 9 and 19 months he had not gained any weight and remained very irritable. Our first physical examination at 19 months showed a small, thin child, weighing 15 pounds. The pulses were of normal volume, and the blood pressure was 98/64. The heart was not enlarged. There was no thrill. Auscultation revealed a very loud first sound, an accentuated pulmonic second sound and a moderately loud systolic murmur at the lower left sternal border; a diastolic murmur was thought to be present at the apex, but this could not be determined with certainty. The *electrocardiogram* showed a pattern of right ventricular hypertrophy. The P waves were tall and peaked in leads II, aV_F, and V_1. On *fluoroscopy*, the heart was not definitely enlarged and no selective enlargement of any chamber could be distinguished. There was a diffuse increase in the hilar vascular markings but no evidence of increased blood flow to the lungs.

He continued to do poorly, and, at 26 months of age, was readmitted in severe congestive heart failure which had appeared suddenly and which responded well to therapy. The heart had enlarged considerably since the previous examinations and auscultation revealed an inconstant diastolic rumble at the apex. Periodic episodes of paroxysmal dyspnea occurred, and, following one of these attacks, cyanosis of the left hand and lower extremities was noted. This differential cyanosis was transient and recurrent. On *cardiac catheterization*, the catheter passed from the pulmonary artery into the descending aorta through a patent ductus. The pressure in the pulmonary artery was of systemic level. At the time of catheterization, there was only a slight amount of venous shunt into the descending aorta, the oxygen saturation of blood in the right radial artery was 92 per cent, and in the descending aorta 85 per cent.

In view of the child's desperate condition, it was decided to attempt ligation of the patent ductus. There was no evidence of cardiac embarrassment following occlusion of the ductus, and no murmur was present postoperatively. The child appeared to be doing well when, suddenly, on the second postoperative day, he developed marked dyspnea and tachycardia and died.

Anatomic Diagnosis. Mitral stenosis and patent ductus arteriosus (successfully closed at operation).

Comment. The remarkable feature of this case was the marked physical and develop-

mental retardation produced by the cardiac lesions, of which the mitral stenosis was undoubtedly the major one. This occurred in the absence of any significant cardiac enlargement. The occurrence of pulmonary edema and the inconstant diastolic murmur at the apex had suggested the possibility of mitral stenosis, but it was felt that there was not enough evidence to substantiate this diagnosis, and the disappearance of all murmurs following operation lent reassurance to this thought. It must be emphasized that the failure to make the correct diagnosis was in a large measure due to the fact that one is not accustomed to think of mitral stenosis as a major possibility among congenital malformations of the heart.

Case 2. B. R. was an 11 month old male child who had done poorly since birth, there being rapid respiration, difficulty in feeding, weakness and developmental retardation. At 10 months of age, he developed pneumonia and was admitted to another hospital where a diagnosis of patent ductus arteriosus and congestive heart failure was made. He responded well to digitalis and antibiotic therapy and was referred to this hospital for operation. The day before admission, he refused feedings, became feverish and restless and, on arrival, was moribund, showing grayish cyanosis, respiratory distress and evidence of peripheral circulatory collapse. He improved somewhat under energetic therapy. The pulses became forceful and collapsing in type. Blood pressure was 104/30. The heart was enlarged and a machinery-like continuous murmur was audible at the upper left sternal border, accompanied by a thrill. The pulmonic second sound was accentuated. Coarse râles were audible over the entire chest; the liver was just at the costal margin. X-ray films of the chest showed a large heart with increased hilar vascular markings and extensive atelectasis of both lower lobes. Evidence of peripheral circulatory collapse recurred and the baby died within 24 hours of admission.

Anatomic Diagnosis. Mitral stenosis and patent ductus arteriosus.

Comment. On clinical examination, this baby appeared to have the typical findings of a patent ductus with circulatory failure.

Case 3. D. O., a 3 week old male infant, had been observed to have rapid respirations since birth and ate poorly. Since the age of 11 days he had had a cough, and his condition deteriorated rapidly. On admission, he was extremely ill, dyspneic and edematous, but not definitely cyanotic. The lungs were filled with fine moist râles and the liver was enlarged to the level of the umbilicus. The heart was grossly enlarged. There was no thrill. A long, rough systolic murmur of moderate intensity was audible in the pulmonary area and transmitted to the back. An *electrocardiogram* showed right axis deviation and a QRS pattern of right ventricular hypertrophy within normal limits for the infant's age. The T waves were inverted in leads I, II, aV_L, aV_F and in all chest leads. The P waves were not abnormal. *X-ray* films showed a grossly enlarged heart and increased hilar vascular markings. Despite digitalis and supportive therapy, his condition deteriorated and he died two days after admission. No definite diagnosis of the cardiac lesion had been made.

Anatomic Diagnosis. Congenital mitral stenosis of a mild degree, aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus (questionably closing).

Case 4. A. C. The history of this 13 month old female child is incomplete, but it appears that her development was poor, and she showed difficulty in breathing. On examination at 11 months of age, there was no cyanosis. The heart was enlarged, and a systolic thrill and murmur were present at the upper left sternal border, the murmur being transmitted to the great vessels of the neck. The liver was slightly enlarged. X-ray films showed marked cardiac enlargement. No definite diagnosis was made. Two months later she was admitted to the hospital, severely ill, and died within one hour.

The late Dr. Maude Abbott examined the specimen and confirmed the *anatomic diagnosis* of moderate congenital mitral stenosis, aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus distal to site of coarctation.

Case 5. D. G. was a 25 month old boy who did well until 8 months of age when he had a sudden attack of respiratory distress and, following this, breathed more heavily and faster than before. He also had a chronic cough. During the month preceding admission to the hospital, he became listless and developed swelling of the face. On examination, he was a fairly well developed child in moderately severe congestive failure. The blood pressure in the arms was 120/80. The femoral pulses could not be felt. The heart was enlarged. There was a systolic thrill and a moderately loud, harsh systolic murmur just inside the apex. No diastolic murmur could be elicited. An *electrocardiogram* showed evidence of marked right ventricular hypertrophy. *Fluoroscopy* showed a greatly enlarged heart, and the hilar vascular markings were increased. There was no evidence of selective enlargement of the left atrium. The clinical diagnosis of coarctation of the aorta was made and it was believed that this was complicated, probably, by a patent ductus located distal to the site of coarctation, and by pulmonary hypertension, which accounted for the right ventricular hypertrophy observed in the electrocardiogram. An *angiocardiogram* showed an essentially normal

TABLE 2.—*Clinical Findings*

No.	Mitral stenosis associated with	Age	Weight	Onset sympt.	Cardiac failure		Murmurs:		E.C.G.		Card. enl.	Death
						Pulm. Ed.	Syst.	Diast.	Hypertrophy	P waves		
1 J. H.	Patent ductus	26 mos.	15 lbs	9 mos.	+	+	+	Trans-ient	R.V.H.	+ Leads 2, V_1	+ Terminal	Postop.
2 B. R.	Patent ductus	10 mos.	10 lbs	birth	+	−	Continuous		Not taken		+	Periph. collapse
3 D. O.	Patent ductus, aortic stenosis, mild coarct. aorta	24 days	9¼ lbs	birth	+	−	+	−	R.V.H.	Normal	+++	C.H.F.
4 A. C.	Patent ductus, aortic stenosis, coarct. of aorta	13 mos.	?	?	−	−	+	−	Not taken		+	?
5 D. G.	Subaortic stenosis, coarct. of aorta, patent ductus	25 mos.	24 lbs	8 mos.	+	?	+	−	R.V.H.	Normal	+++	Op.
6 M. L.	Aortic stenosis, patent for. ovale	7 weeks	7½ lbs	birth	+	?	+	−	R.V.H.	Normal	+++	?
7 H. B.	Aortic stenosis	16 mos.	23 lbs	? birth	−	?	+	−	Not taken		No X-ray	Pneum.
8 C. R.	Vent. sept. def., overr. aorta	10½ mos.	14 lbs	birth	−	−	−	−	R.V.H.	+ Lead 2	No X-ray	Cyan. attack
9 C. S.	Double aortic arch	3½ mos.	9 lbs	3 mos	+	?	?	−	Not taken		+++	Pneum.

Abbreviations: R.V.H. = Right ventricular hypertrophy. C.H.F. = Congestive heart failure.

course of the circulation, but dye returning to the left side of the heart was held up in the left atrium and, only in the last film, taken eight seconds after injection, was the aorta visualized. This finding suggested the possibility of an associated mitral stenosis. At *operation*, the coarctation of the aorta was resected. A small ductus, believed to be closed, entered the aorta just distal to the coarctation. The child died suddenly at the end of operation.

Anatomic Diagnosis. Severe stenosis of the mitral valve. Incomplete subaortic stenosis, coarctation of the aorta (successfully resected), and probe patency of the ductus arteriosus.

Comment. In this case the existence of mitral stenosis with coarctation of the aorta was recognized preoperatively on the basis of the angiocardiographic findings, but the severity of this lesion and its serious consequences were not appreciated.

Case 6. M. L., a 7 week old infant girl, had done poorly since birth, there having been great feeding difficulty and failure to thrive. One week prior to admission, she developed a cold and difficulty in breathing. On arrival in hospital she was acutely ill, cyanotic and dyspneic. Râles were heard over the left lung field. The heart was enlarged. A slight thrill was palpable at the upper left sternal border associated with a harsh systolic murmur. The liver was enlarged two fingerbreadths below the costal margin. An *electrocardiogram* showed a pattern of right ventricular hypertrophy and inverted T waves in all standard leads and in aV_L and aV_F, and upright T waves in the chest leads. *Fluoroscopic* examination revealed a grossly enlarged heart and evidence of pulmonary congestion. No area of pneumonic consolidation was identified. The left atrium was not enlarged. The baby responded to oxygen, digitalis and antibiotic therapy and the cyanosis disappeared. Three weeks later, her condition deteriorated somewhat and, on the twenty-sixth hospital day, she suddenly developed marked respiratory distress and died. No definite diagnosis of the cardiac lesion had been made.

Anatomic Diagnosis. Mitral stenosis of slight degree, severe aortic stenosis, patent foramen ovale.

Case 7. H. B., a 16 month old male infant, was brought to the hospital in a moribund state and died within one hour. A detailed history is not available. He was never well, suffering from frequent attacks of "asthma" since early infancy. For several days before admission to the hospital, he had a cold and increasing shortness of breath. As this was apparently a frequent occurrence, the parents showed no concern until he became severely distressed. On examination, he was well developed and well nourished, slightly cyanotic, and in extreme respiratory distress. There was a marked

FIG. 1. Mitral valve in case 5, showing severe stenosis with malformation and fusion of the leaflets and the chordae tendineae. Note the double orifice. The left ventricular myocardium shows marked hypertrophy.

inspiratory stridor and dullness to percussion over the upper lobes of the lungs but no râles. The heart appeared to be enlarged and a soft systolic murmur was heard at the apex. The liver was not enlarged. He was given oxygen, antibiotics and a small dose of adrenaline, but respirations ceased soon after admission and all resuscitative efforts failed. No definite diagnosis was made.

Anatomic Diagnosis. Moderate degree of mitral stenosis and aortic stenosis.

Case 8. C. R., a male infant, was first seen at the age of 10½ months when he was admitted to the hospital and died 12 hours later. He had a "poor color" after birth and, by 1 month of age, was considered to be definitely cyanotic. He always breathed forcefully and with difficulty. He fed poorly and his development appeared retarded. For two weeks prior to admission he had a cough, and a diagnosis of bronchopneumonia was made at another hospital. One week before admission to the hospital, he began to have attacks of severe cyanosis in which he became stiff and unresponsive. On the day before admission, he had seven such spells. On examination, he appeared ill and underdeveloped, weighing 14 pounds. He showed moderate cyanosis with early clubbing of the fingers and toes. Respirations were rapid with subcostal indrawing, but there were no râles. The heart sounds were of good intensity and no murmur was present. The liver was 3 cm. below the costal margin. Shortly after admission, he had

TABLE 3.—*Pathologic Findings*

	Case 1 (A.52-147) 26 mos.	Case 2 (A.53-4) 10 mos.	Case 3 (A.51-66) 24 days	Case 4 (A.39-57) 13 mos.	Case 5 (A.51-80) 25 mos.	Case 6 (A.50-2) 7 weeks	Case 7 (A.52-117) 16 mos.	Case 8 (A.49-36) 10½ mos.	Case 9 (A.45-102) 3¼ mos.	Total No.
Mitral Stenosis	+++	++	+	++	+++	+	++	+++	++	9
Right Atrium										
Dilatation	++	—	+	+	++	++	+	++	—	7
Hypertrophy	++	—	—	+	+++	+	+	+	—	6
Endocardium	—	—	—	Sl. opaque	Sl. opaque	—	Sl. opaque	—	—	3
Left Atrium										
Dilatation	+	+	—	—	—	+	+++	++	+++	6
Hypertrophy	++	+	—	++	+++	+	++	++	+	8
Endocardium	opaque & thick	opaque & thick	—	opaque & thick	opaque & thick	Sl. opaque	opaque & thick	opaque & sl. thick	Sl. thick	8
Right Ventricle										
Dilatation	++	+	+	+	++	+	+	+	—	8
Hypertrophy	+++	+	++	+	+++	+	++	+++	++	9
Left Ventricle										
Dilatation	—	++	—	++	small cavity	+	—	small	—	3
Hypertrophy	—	+++	+	+++	++	+++	+++	—	+	7
Aortic Valve	normal	normal	stenosis +++	stenosis +++	normal subaortic shelf	stenosis +++	stenosis ++	small but normal	normal	stenosis 4
Pulmonary Valve	Sl. large	normal. Sl. sclerosis	normal	normal	large. Sl. sclerosis	normal	normal	large. Sl. sclerosis	normal	Sl. "stress" sclerosis 3
Associated Anomalies	P.D.A.	P.D.A.	Aortic stenosis; mild coaret. of aorta; P.D.A. ? closing	Aortic stenosis; mild coaret. of aorta; P.D.A. 6 mm. diam. distal	subaortic shelf; coaret. of aorta; P.D.A. probe patent distal	Aortic stenosis; P.F.O. 5 mm. diam.	Aortic stenosis	Basilar I.V.S.D. Sl. overriding of aorta	Double aortic arch with sten. left arch	
Vascular changes	Mod. medial hypertrophy; sl. atheroscler. of elast. vessels	slight	Muscular arteries in fetal state	None	Marked med. hypertrophy; sl. atherosclerosis of elast. vess.	Muscular arteries in fetal state	Sl. medial hypertrophy	Sl. medial hypertr. El. art. normal	Muscular arteries in fetal state	8
Lungs										
Congestion	+	+	+++	+	+++	+	++	+++	+	9
Edema	—	+	—	—	—	—	—	—	—	1
Heart failure cells	+++	—	—	+	++	—	++	+	+	6

Grading: + = slight; ++ = moderate; +++ = marked.

an attack of extreme cyanosis with gasping respirations, and distant, slow and irregular heart sounds. The eyes were fixed and the corneal reflex was absent. Oxygen, morphine and adrenaline were given. There was a striking improvement in color shortly after the administration of oxygen was begun with almost complete disappearance of the cyanosis. Respirations remained labored and grunting for some time. A few hours later a similar attack occurred and the infant died in spite of vigorous therapy. The *electrocardiogram* showed a pattern of marked right ventricular hypertrophy. The P waves in lead II were 3 mm. tall and pointed. In view of the infant's desperate condition, an x-ray film was not made. No definite diagnosis was possible.

Anatomic Diagnosis. Marked mitral stenosis. High basilar ventricular septal defect with slight over-riding of the aorta.

Comment. It is remarkable that this infant had cyanotic attacks similar to those seen in cases of tetralogy of Fallot and he died in such a spell. A dramatic improvement in color followed the administration of oxygen in one of these attacks.

Case 9. C. S. This infant girl was 3½ months old. A heart murmur was noted shortly after birth, but the baby did well until the age of 3 months when she developed wheezing respirations and a cough. She became increasingly restless and, on the day of admission, had a severe coughing spell with "froth coming from mouth." On examination, the baby was small, weighing 9 pounds. Respirations were rapid. There were signs of consolidation over the right lung. A murmur was not clearly audible. The liver was enlarged 2 fingerbreaths below the costal margin. X-ray films showed a grossly enlarged heart and evidence of a right upper lobe pneumonia. She received chemotherapy, but her course was downhill and she died on the tenth hospital day. The clinical diagnosis was congenital heart disease with increased blood flow to the lungs, congestive heart failure and pneumonia.

Anatomic Diagnosis. Moderate mitral stenosis and double aortic arch.

Pathologic Findings

The pathologic findings are summarized in Table 3. The mitral lesion was characterized by short, thickened, fused and deformed chordae tendineae with endocardial thickening of the apexes of the papillary muscles. In the cases in which there was moderate or marked stenosis, the leaflets were thickened but differed from the leathery scarring of acquired lesions by their semitranslucent, pearly appearance. They were often semicartilagenous in consistency with slightly fluted edges. The chordae were fused into the leaflets. In the two instances of mild stenosis, the leaflets were practically normal, but the chordae were short, fused, and thickened and, on stretching the valves, they appeared somewhat shelf-like and did not flatten out against the ventricular wall. The orifice was usually funnel-shaped, and the circumference of the valve ring was approximately normal except in the instances of marked stenosis.

The endocardium of the left atrium showed well marked thickening in six instances, slight opacification in two, and a normal appearance in one. This change appeared to be correlated with age and with the severity of the mitral stenosis. All of the first six were over 10 months of age and showed moderate to marked stenosis; two were aged 3½ and 1½ months and showed moderate and slight stenosis, respectively, while the last was 24 days and had slight stenosis. It has been suggested that a stenotic lesion of the mitral or tricuspid valve may lead to "stress" thickening of the atrial endocardium.[32a, 41] In this connection, it is of interest that obstructive lesions of the gall bladder give rise to hypertrophy and hyperplasia of the elastic tissue in the wall of this organ.[42] The apparent progression of endocardial changes with age in our cases suggests that the duration of the effect of the obstructive lesion played a definite role in the development of the atrial endocardial fibroelastosis. In the light of this evidence, the endocardial changes are unlikely to be of congenital origin. None of the other chambers of the heart showed gross or microscopic evidence of endocardial fibroelastosis, except in one instance (case 7). The fibroelastosis of the left ventricle in this case is believed to be related to the presence of aortic stenosis as there was fairly extensive myocardial atrophy and collapse fibrosis.

There was no strict correlation between the degree of mitral stenosis and dilatation of the left atrium, but there was a reasonable relationship as regards hypertrophy. In comparing the thickness of the right ventricle with that in normal controls, it was evident that right ventricular hypertrophy of varying degree

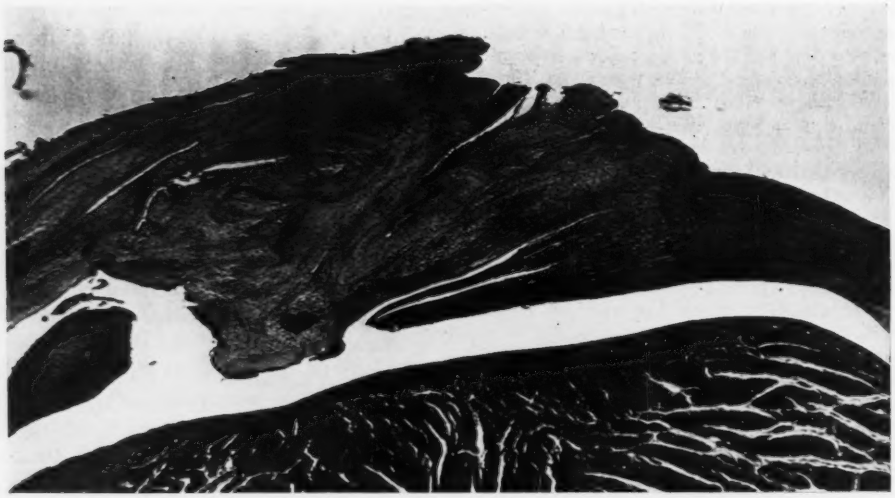


FIG. 2. Longitudinal section of the posterior mitral leaflet in case 5. The base of the leaflet is to the right and is normal in appearance. The distal half of the leaflet and the chordae form a confused mass, much of which is loose mesenchymatous tissue. (Masson trichrome stain. × 30)

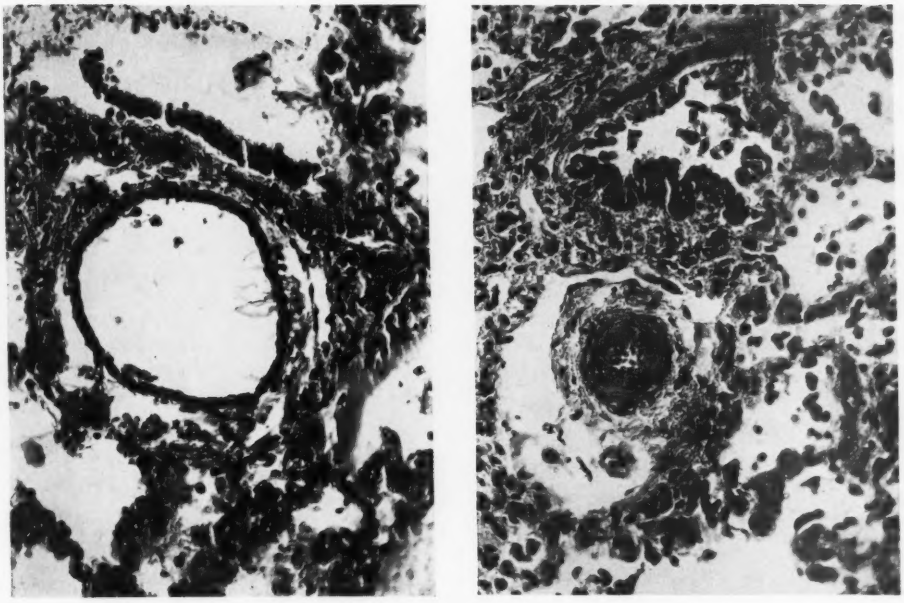
was present in all cases. Left ventricular hypertrophy was present in four cases complicated by aortic stenosis, in one with coarctation of the aorta and a subaortic shelf, and in one case in which the associated lesion was a patent ductus arteriosus.

On microscopic examination, there was no evidence of inflammation or scarring in numerous sections of the heart. In the cases with stenosis of the aortic valve, atrophy of muscle fibers with replacement fibrosis (ischemic) of varying degree was observed. The mitral valves (fig. 2) did not show scarring but presented an abnormal and confused pattern of the layers. Cellular mesenchymatous tissue predominated and was mixed in a most irregular manner with dense collagenous tissue which resembled the ventricularis layer. The basilar part of the leaflet was often normal, the malformation of the layers involving the distal half of the leaflet and the chordae tendineae.

Pulmonary vascular changes were assessed by comparison with normal controls, and no measurements of lumen and wall thickness were made. There were no intimal changes. In the two older cases (1 and 5) medial hypertrophy of the muscular arteries was marked (fig. 3) and was accompanied by mild atherosclerotic changes in the elastic vessels. In case 5, the only apparent cause for these changes was the presence of mitral stenosis. In case 1, although a patent ductus was also present, the severity of the vascular changes was such as to lead one to believe that the presence of marked mitral stenosis played a major rôle in their genesis. In cases 3, 6 and 9 (3½, 7 and 14 weeks old, respectively) the muscular arteries showed the appearance characteristic of the "fetal state." In the absence of absolute criteria for the end of the fetal state, these changes may be abnormal for these infants. While this cannot be stated with certainty, the presence of right ventricular hypertrophy may be suggestive evidence of this. The muscular arteries showed definite medial hypertrophy in cases 7 and 8 and borderline changes in case 2. In case 4 the pulmonary vasculature appeared entirely normal.

PREVIOUS REPORTS OF CONGENITAL MITRAL STENOSIS IN THE LITERATURE

A search of the literature has yielded 3[illegible] cases of congenital mitral stenosis (table 4) present as an isolated malformation in 8 and



A *B*

FIG. 3. Sections of lung showing muscular artery at about the commencement of a respiratory bronchiole. (H & E stain × 200) (*A*) Normal control of same age as case 5. (*B*) Case 5. Note marked medial hypertrophy, small lumen and dense adventitia.

associated with other defects in 26. In the reported cases of Lutembacher's syndrome,[2b, 26-32] a rheumatic origin of the mitral stenosis could not be excluded in any instance and, thus, no such case appears in this series. Of the 34 cases comprising this group, all but one were under 3 years of age and 16 were less than 6 months old.

A review of the histories and physical findings reveals no definite diagnostic criteria but supports certain observations made in connection with our own series. There were eight patients who appeared well in early infancy and had a sudden onset of symptoms between 8 months and 2½ years of age. Cough, dyspnea and congestive heart failure were common. Cyanosis was mentioned in 15 instances, but, at least in some, this may have been terminal and associated with congestive failure. Two patients had differential cyanosis involving the lower extremities, owing to reversed flow through a patent ductus. Accentuation of the heart sounds was rarely clearly described, but two were noted to have had accentuation of the mitral first sound and three of the pulmonic second sound. Five patients were stated to have no murmur. In 12 cases the presence of a diastolic murmur was mentioned; in two of these the murmur was at the left sternal border, in eight the murmur was described as apical or presystolic and in two the location of the murmur was not specified. Electrocardiographic findings were noted in five cases. Three showed a precordial pattern of right ventricular hypertrophy; in two, right axis deviation only was commented upon; P waves were broad and notched in only one instance, tall and pointed in two. Angiocardiographic evidence of mitral stenosis was observed in three cases.[23, 24, 25]

Recent reports emphasize the severity of the pulmonary vascular changes and the disappointing results of otherwise successful surgical correction of coarctation of the aorta and patent ductus because of the presence of mitral stenosis. A mitral valvulotomy was performed in one patient 9½ months of age, reported by Bower and co-workers.[24] These authors have

TABLE 4.—*Summary of Cases of Congenital Mitral Stenosis Reported in the Literature*

Case No.	Year	Reference	Age	History	Physical findings	Investigation	Pathology		
							Associated malform.	Endocardium	Microscopic
1	1846	Smith[1]	21 hrs.	Cyanosis at birth; dyspnea; "apoplexy"	—	—	P.D.A.—large	—	—
2	1885	Ayrolle[2]	10 days	Dyspnea; cyanosis	—	—	?	—	—
3	1894	Carmichael[3]	36 mos.	Dyspnea on feeding; bronchitis; cyanosis	Split sounds; no murmurs	—	Coarc. of aorta; P.D.A. into desc. aorta	—	—
4	1900	Cotton[4]	5 days	Cyanosis 1st day	Harsh diast. murmur	—	Defective aortic valve (insufficient); P.D.A. large; P.F.O.	—	—
5	1902	Fisher[5]	15 mos.	Cyanosis at birth; attacks of dyspnea; small size	Syst. murmur; triple sound at apex	—	Coarc. of aorta; P.D.A.—pinpoint	—	—
6	1906	Summons[6]	19 mos.	Dyspnea and cyanosis since birth	Thrill; syst. and presyst. murmurs at apex	—	None	—	—
7	1907	Kockel[7]	4 hrs.	—	—	—	Aort. sten.	—	—
8	1911	Fischer[8]	5 wks.	Slight cyanosis; weakness; edema	—	—	Aort. sten. P.F.O.	—	—
9	1912	Ludwig[9]	Newborn	Generalized edema	—	—	P.D.A. — small probe	Thin	—
10	1924	Donnelly[10]	3 days	Sudden attack of dyspnea	Syst. murmur at base and back	—	Hypoplastic aorta; P.D.A.—large; P.F.O.	—	—

11	1932	Day[11]	24 mos.	Well to 10 mos; dyspnea; cough; poor feeding	Edema; diast. thrill and murmur at apex; short syst. murmur; Accent. P_2.	—	None	Thick in L.A. and R.V.	No Aschoff bodies; lungs: thick alveolar walls
12	1933	Farber et al.[12]	3 days	Cyanosis and dyspnea since birth	No murmur	—	Aort. sten. P.D.A. — large; P.F.O.	Thick in L.V.	Thick endocard; no inflammatory cells
13	1935	McIntosh et al.[13]	34 mos.	Bronchopneumonia at 21 mos.	Soft syst. murmur; card. failure	—	None	Thick plaques in L.A.	Fibrosis "healed process"
14	1938	Newns[14]	21 mos.	Anemia; dyspnea; no cyanosis	Loud M_1; presyst. apical murmur; card. failure	—	Bicuspid aortic valve	—	—
15	1938	Fields[15]	4 mos.	Dyspnea; cyanosis	Loud M_1; presyst. apical murmur	—	Aplasia left side of heart	—	—
16		Fields[15]	10 mos.	—	Apical syst. murmur	—	P.D.A; aplasia left side of heart	—	—
17		Fields[15]	4 days	Cyanosis	—	—	Bicusp. aortic valve; small asc. aorta; P.D.A; P.F.O.	—	—
18		Fields[15]	3½ mos.	Cyanosis; dyspnea	—	—	I-V septum almost absent; P.F.O.	—	—
19	1941	Gross[16]	4 days	Sudden cyanosis and dyspnea	—	—	P.D.A. — large; aort. sten.	Thick in L.A. and L.V.	Fibroelastic endocard; no inflammatory cells

TABLE 4.—*Continued*

Case No.	Year	Reference	Age	History	Physical findings	Investigation	Pathology		
							Associated malform.	Endocardium	Microscopic
20	1945	Johnson et al.[17]	33 mos.	Pertussis and card. failure at 2½ yrs.	Syst. and presyst. murmur at apex.	—	Aort. sten.	Thick in L.A.	Fibrous scarring of endocard
21	1949	Craig[18]	4 mos.	Feeding difficulty	No murmur	—	None	Thick in L.V.	Fibroelastic endocard; slight muscular degeneration
22		Craig[18]	7½ mos.	Feeding difficulty; cyanosis	Loud syst. and diast. murmur	—	Deformed tricuspid valve	Thick in L.A. and L.V.	Fibroelastic endocard; slight muscular degeneration
23	1949	Swan et al.[19]	18 yrs.	Dyspnea; underdeveloped; card. failure; died during operation for coarc. & P.D.A.	Syst. and diast. murmur in pulmon. area; accent. P_2; cyanotic toes	E.C.G: Prom. P waves; R.A.D; card. cath.	Coarc. of aorta; P.D.A. into desc. aorta	Normal	Severe pulm. vasc. changes
24	1950	McConnell[20]	19 mos.	Well to 18 mos; weakness & dyspnea; terminal cyanosis	Syst. murmur at apex & rt. sternal border. card. failure	—	Tricuspid sten; aortic sten.	Thick	Fibrosis of myocard; no inflammatory cells
25	1951	Emery et al.[21]	36 mos.	Well to 2 yrs. cough; dyspnea	No murmur; card. failure; heart not enl.	—	None	Pale in L.A.	Collagenous thick endocard; no inflammatory cells
26		Emery et al.[21]	18 mos.	Well to 17 mos. cough; bronchopneumonia and card. failure	Syst. and loud diast. murmur at apex; enl. heart only terminally	E.C.G: R.A.D.	Aortic valve, thickened edge; P.D.A. pinpoint	Thick in L.A.	Collagenous thick endocard; no inflammatory cells
27	1952	Blumberg et al.[22]	Newborn	Cyanosis; respiratory distress	—	—	Aort. sten; P.D.A; P.F.O. —physiol.	Thick in L.A. and L.V.	Areas of degen. and calc. in myocardium

28		Blumberg et al.[22]	4½ mos.	Cyanosis since birth; card. failure	Loud syst. and diast. murmur at left sternal border	—	Aort. sten. P.D.A.	Thick in L.A. and L.V.	Areas of degen. and fibrosis in myocardium
29		Blumberg et al.[22]	16 mos.	Well to 15½ mos; pneumonia; card. failure	No murmur	—	Thickening of aortic and pulm. valves	Thick in L.A. and L.V.	Fibroelastic tissue of endocard.
30		Blumberg et al.[22]	16 mos.	Dyspnea and card. failure since 8 mos.	Syst. murmur at apex	—	None	Thick in L.A. and L.V.	Fibroelastic tissue of endocard. invading myocardium
31	1953	Azevedo et al.[23]	18 mos.	Dyspnea & fatigue; pneumonia; card. failure; died after ligation P.D.A.	Diast. rumble at apex; accent. split P_2; slight cyanosis of toes	E.C.G: R.V.H. Prom. P waves; card. cath; angiocard.	P.D.A.	—	Marked pulm. vasc. changes
32	1953	Bower et al.[24]	9½ mos.	Poor feeding; cough; card. failure; died after mitral valvotomy	Presyst. thrill and murmur; syst. murmur	E.C.G: R.V.H. Prom. P. waves; card. cath; angiocard.	None	Thick in L.A. and L.V.	Fibroelastosis of endocard; pulm. vasc changes
33		Bower et al.[24]	2 mos.	Death before studied		None	None	Thick in L.A.	Fibroelastosis of endocard.
34	1953	Jacobson et al.[25]	24 mos.	Dyspnea; poor development; died during operation for coarc. of aorta	Syst. murmur at rt. and left sternal borders; absent fem. pulsat.	E.C.G: R.V.H. angiocard.	Coarc. of aorta	Thick in R.V. and L.V.	

Abbreviations: P.D.A. = patent ductus arteriosus; P.F.O. = patent foramen ovale; L.A. = left atrium; L.V. = left ventricle; R.V. = right ventricle; R.V.H. = right ventricular hypertrophy; R.A.D. = right axis deviation; — = no record.

also operated upon a 5½ year old girl who is still living.

Circulatory Arrangements Associated with Mitral Stenosis

Congenital mitral stenosis may cause severe hemodynamic alterations and the development of hypertensive pulmonary vascular changes which affect adversely the course and prognosis of otherwise more benign or correctable malformations.

Taussig[33] has pointed out that, in congenital mitral stenosis, hypertrophy of the right side of the heart may occur in fetal life. If the pressure in the left atrium is elevated, the normal right-to-left shunt through the foramen ovale is reduced, and most of the blood returning from the placenta reaches the systemic circulation by passing through the right ventricle, pulmonary artery and, via the patent ductus, into the aorta. The malformations usually associated with mitral stenosis should not alter this fetal circulatory arrangement significantly. The blood flow through the left side of the heart thereby being reduced, areas of stenosis in the aortic or subaortic regions are to a great extent bypassed. Following birth, however, the presence of other lesions can modify the effect of mitral stenosis in different ways. While the combination of defects may be variable, essentially three different arrangements may occur (fig. 4):

1. Mitral stenosis occurs alone or in association with an obstructive lesion of the left side of the heart or the aorta (that is, aortic stenosis or coarctation of the aorta). The pulmonary vascular changes are apparently due to mitral stenosis. The pulmonary pressure is increased, the pulmonary flow is reduced, and there is no shunt. Case 5 falls into this group.

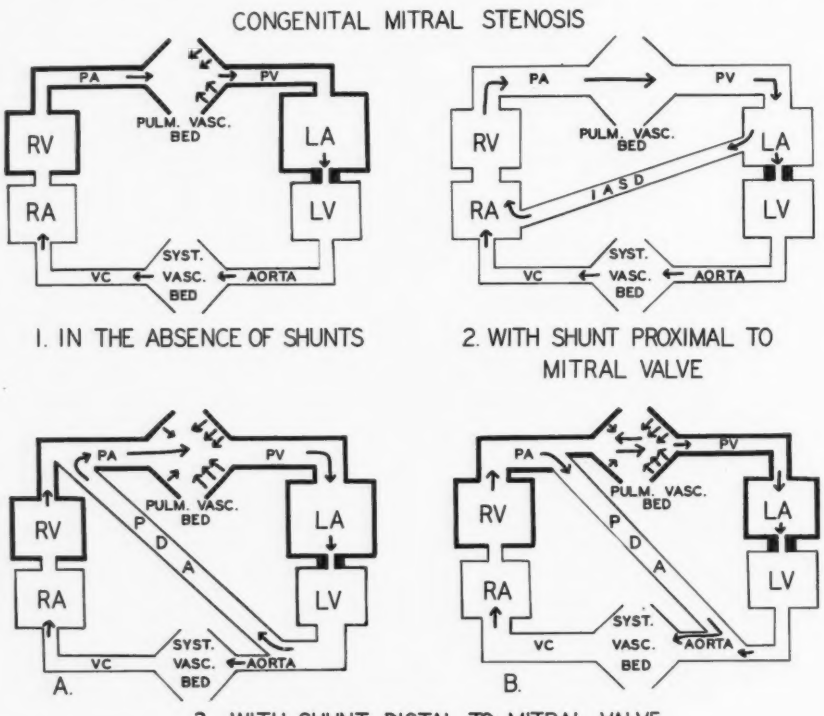


Fig. 4. Circulatory alterations in congenital mitral stenosis. See text. Heavy lines indicate areas of increased pressure. Size of vessels drawn to indicate amount of blood flow.

Resection of the coarctation in this instance removed the last of a series of obstructions while the major lesion remained.

2. Mitral stenosis is associated with a defect proximal to the mitral valve allowing a left-to-right shunt to occur, for example, interatrial septal defect. This shunt reduces the pressure in the left atrium and the usual effect of mitral stenosis upon the pulmonary vascular bed is therefore relieved. The pulmonary flow is increased, but, as the pulmonary vascular bed is essentially normal and can passively accommodate a large flow of blood, severe pressure changes do not occur. This arrangement is found in Lutembacher's syndrome. A similar effect has been produced surgically by shunting operations between pulmonary and systemic veins for the relief of acquired mitral stenosis.[34]

3. Mitral stenosis is associated with a defect distal to the mitral valve (patent ductus or interventricular septal defect) and a shunt can occur in either direction, depending upon the relative resistances in the systemic and pulmonary circulations. If, as in the case of a patent ductus, the shunt occurs in the usual fashion from aorta into pulmonary artery (figs. 4, 3*A*), the lungs are exposed not only to the back pressure due to mitral stenosis, but also to a large pulmonary blood flow under elevated pressure, and both of these factors would promote arterial thickening. The larger amount of blood having to pass through the narrowed mitral valve accentuates the effect of the stenosis. It may be hoped that ligation of the ductus may lead to improvement by reducing the amount of blood which must pass through these two areas of high resistance. If the pulmonary vascular changes are severe, the amount of blood which the lungs can accommodate is reduced and the shunt through the patent ductus may become reversed (figs. 4, 3*B*). When this occurs, the ductus acts as an escape mechanism and any further increase in pressure will lead to a larger amount of blood passing from pulmonary artery into aorta. At this time ligation of the ductus offers no improvement and is probably contraindicated. In case 1, reversal of flow through the ductus was only intermittent, and it was hoped that the pulmonary vascular changes might still be reversible. In case 8, a patient who died in a cyanotic attack, the circulatory arrangement may have been of a similar nature. In this instance, again, there were two lesions, the interventricular septal defect with over-riding aorta and mitral stenosis, additive in their effect in promoting pulmonary vascular changes. The narrowed pulmonary bed acted in a fashion similar to a pulmonic stenosis and prevented blood from entering the lungs. Thus, the ventricular septal defect acted as an escape mechanism and an excessive flow of venous blood was directed into the systemic circulation.

Discussion

An analysis of nine cases found in the records of The Children's Memorial Hospital and of 34 cases from the literature would indicate that congenital mitral stenosis is not so rare a lesion as it is at present considered to be. Our nine cases were encountered in the course of 2067 consecutive autopsies performed since 1934, among which were 210 cases of congenital heart disease, representing an incidence of 0.43 per cent in the total series and 4.3 per cent of cardiac malformations. Associated malformations of the heart and the great vessels were frequently present. Among the 43 cases under discussion, there were only eight instances of isolated mitral stenosis. An analysis of the associated lesions reveals a high incidence of malformations involving the aortic valve, the aorta and ductus arteriosus. There were only two cases of associated ventricular septal defect, and we have not yet discovered a case of mitral stenosis, undeniably of congenital origin, associated with a significant defect of the interatrial septum. This fact may lend support to the opinion[2b, 30] that the mitral stenosis of Lutembacher's syndrome is acquired. Apparently, defects of the atrial, ventricular, and aortic septa rarely occur with mitral stenosis. The embryologic significance of this fact is a matter of conjecture. The earlier reports in the literature have been concerned with a controversy

regarding the occurrence of intrauterine inflammatory processes and their possible relationship to valvular malformations, but the theory of "fetal endomyocarditis" appears to have been disproved by later work based on careful microscopic study.[12, 16] Craig,[18] in a study of cases of congenital heart disease with ventricular endocardial thickenings, pointed out the association of valvular lesions and the rarity of septal defects. He considered these lesions to be the result of a developmental abnormality consisting in an overproduction of tissues arising from the endothelial layer involving also, therefore, the closing masses of the various communications between the two sides of the heart. It is not the purpose of this paper to enter into a discussion of embryologic theories, but merely to point out that the selective association of certain malformations with congenital mitral stenosis may represent significant evidence for the future elucidation of the nature of these lesions.

Of the 43 cases under discussion, all but one died under 3 years of age This finding testifies to the severe consequences of this malformation, for, in most instances, the associated defects (table 1) did not appear severe enough to be responsible for death at such an early age.

An analysis of the histories and physical findings has yielded no definite diagnostic criteria, but certain features of importance have become apparent. Eleven patients showed good health in early infancy and a sudden onset of symptoms, usually respiratory distress, at varying ages between 3 months and 2½ years. This sudden onset of symptoms may be associated with the progressive hypertensive changes in the pulmonary vascular bed which, having reached a certain degree, precipitate the patient's rapid downhill course.

Cyanosis, often terminal, was observed in 19 instances and there were three cases of differential cyanosis involving the lower extremities due to shunting of blood from pulmonary artery to aorta through a patent ductus. Such reversal of blood flow may occur through a patent ductus present as an isolated malformation[35-39] but complicated by pulmonary hypertension. As mitral stenosis is responsible for the development of severe pulmonary vascular changes and consequently a high pulmonary resistance, its presence should be considered when reversal of blood flow through a patent ductus is observed. From a consideration of the hemodynamic alterations imposed by mitral stenosis in the presence of defects distal to the mitral valve it would appear that a significant degree of cyanosis in these cases is indicative of severe pulmonary vascular changes and a grave prognosis.

The auscultatory finding of an apical diastolic murmur, so characteristic of acquired mitral stenosis, was rarely present in these cases. Furthermore, the frequency of an apical diastolic rumble in congenital heart lesions in the absence of mitral stenosis is recognized,[40] and the diagnosis of congenital mitral stenosis would be made too frequently if undue attention were directed toward this auscultatory sign. A more significant finding may be the accentuation of both the mitral first and the pulmonic second sounds, but, unfortunately, little attention has been paid to these signs in the histories. In six patients there were no murmurs.

In the electrocardiogram, a pattern of right ventricular hypertrophy was always demonstrated in the precordial leads. The P waves did not contribute helpful evidence of left atrial enlargement, nor was this abnormality satisfactorily detected on fluoroscopic examination. Cardiac catheterization in cases of acquired mitral stenosis usually demonstrates an elevated pulmonary "capillary" pressure. Such a finding may be of diagnostic value in cases of congenital heart disease where mitral stenosis is suspected, if left ventricular failure can be eliminated as its cause. The demonstration of delayed emptying of the left atrium by angiocardiography has provided an important indication of mitral stenosis.

From a consideration of these observations it may be concluded that mitral stenosis should be suspected when the history is suggestive of pulmonary edema, when the clinical picture produced by recognized lesions, such as patent ductus or coarctation of the aorta is atypical and when the electrocardiogram

indicates a disproportionate degree of right entricular hypertrophy.

Microscopic examination of the lungs of the ine cases encountered in this hospital has nown that extensive changes, similar to those und in acquired disease, can be present at an arly age. The structural changes vary with he age of the patient and the degree of mitral tenosis The severe narrowing of the small ulmonary arteries and arterioles observed n a child 2 years of age and illustrated in gure 3 is indicative of the progressive nature f these lesions. It is now well recognized that he presence of pulmonary hypertension and he anatomic alterations produced thereby re of great significance in determining the prognosis in the individual patient. This contention is supported by the early mortality in the group of cases under discussion and furthermore by the serious consequences of surgical correction of an associated lesion.

Surgical treatment of the congenital form of mitral stenosis has been attempted, but only one patient is known to have survived the procedure.[24] A mitral valvulotomy, in cases of isolated mitral stenosis, or a valvulotomy combined with resection of a coarctation or ligation of a patent ductus is doubtless the desirable approach in the treatment of these patients. An evaluation of the structural alterations of the mitral valve observed in our cases suggests that, in congenital stenosis, the entire valve mechanism is affected and the excellent results which attend therapy of the acquired form may not be readily duplicated.

Summary

1. A clinicopathologic study of nine cases of congenital mitral stenosis is presented. This represents an incidence of 4.3 per cent among cases of cardiac malformations encountered in the autopsy records of this hospital.

2. A review of the literature since 1846 has revealed 34 cases.

3. Mitral stenosis occurred infrequently as n isolated malformation. Its association with ortic stenosis, coarctation of the aorta and atency of the ductus arteriosus is significant. Defects of the atrial, ventricular, or aortic epta were rarely present.

4. The diagnosis is difficult. The presence of mitral stenosis should be suspected when the history is suggestive of the occurrence of pulmonary edema, when the clinical picture produced by other lesions, such as coarctation of the aorta or patent ductus, is atypical, and when the electrocardiogram shows evidence of right ventricular hypertrophy in the presence of a recognized left-sided lesion. The finding of an elevated pulmonary "capillary" pressure on cardiac catheterization, and the demonstration of delayed emptying of the left atrium by angiocardiography are features of diagnostic importance.

5. Pathologic findings are noted. The appearance of the mitral valve was similar in all cases, showing thickened leaflets and short fused chordae tendineae, due to an irregular arrangement of cellular mesenchymatous tissue replacing the normal pattern of the endocardial layers. The right ventricle was hypertrophied in all instances. Pulmonary vascular changes were present in all but one case and were of a severe degree in the older patients.

6. Circulatory derangements imposed by mitral stenosis are discussed. If mitral stenosis occurs as an isolated lesion, its effect is similar to that of the acquired form. In association with aortic stenosis or coarctation of the aorta, it is one of a series of lesiòns obstructing the passage of oxygenated blood to the periphery. Its effect may be minimal if the obstruction it presents is relieved by a defect of the interatrial septum. When a patent ductus or an interventricular septal defect is associated, pulmonary hypertensive changes may alter the usual direction of the shunt.

7. The importance of congenital mitral stenosis is stressed because it may complicate a malformation otherwise amenable to surgical therapy and nullify the successful correction of the associated lesion.

Sumario Español

Nueve casos de estenosis mitral congénita se presentan con un repaso de 34 casos de la literatura. Una incidencia alta de malformaciones de la válvula aórtica, de la aorta y del ducto arterioso es aparente. Hallazgos clínicos y resultados de procesos investigativos se han

repasado. Estenosis mitral es responsable por severas alteraciones circulatorias y el desarrollo de cambios hipertenso pulmonar vasculares. La malformación tiene consecuencias serias. Esta asociada con una mortalidad temprana y convierte en inefectiva la correción quirúrgica de coarctación de la aorta y del ducto arterioso patente.

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A Clinical Estimation of the Blood Pressure in the Minute Vessels of the Human Skin by the Method of Elevation and Reactive Hyperemia

I. The Treatment and Prognosis of Necrotic Lesions of the Foot

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The filling pressure in the minute vessels of the skin of the foot has been estimated by a method of elevation and reactive hyperemia. A series of 90 observations was made on 78 patients. This test has been found helpful in evaluating the degree of arterial insufficiency, permitting a more accurate selection of patients to be treated by conservative methods, local amputation or more radical procedures.

IN clinical practice, the development of local necrotic lesions of the foot as the result of circulatory failure alone is rare. These occur more commonly when trauma (physical, chemical or thermal) or infection is superimposed on a previously depressed circulation. But many cases of necrotic lesions of the foot present a problem in prognosis and treatment after all factors other than arterial inflow have been corrected.

The distribution of blood is carried out by the cardiovascular system, but the effective physiologic changes pertaining to the metabolism of the cell occur in the capillary bed. It is at this point that the actual interchange of nutritive and waste substances takes place. These changes occur in relation to the oncotic pressure as balanced against the intraluminal capillary pressure in the presence of a semipermeable membrane. It is, therefore, important to know the pressure under which the blood is delivered to the capillaries in various conditions of health and disease. It seems reasonable to assume that the ability to measure or evaluate capillary pressure might lead to a prophecy of success or failure in regard to cellular nutrition and allow one to select conservative measures or to adopt more radical procedures, such as amputation, in the treatment of necrotic lesions of the foot.

Various indirect methods have been used to measure the intraluminal capillary pressure with resultant figures ranging from approximately 10 to 70 mm. Hg.[1-4] Most of the methods used involved measuring the pressure sufficient to cause blanching or obliteration of the capillaries in the skin. Other methods such as the puncturing of the skin and measurement of the pressure sufficient to control bleeding have been used. The results have varied widely and each method has had imperfections which have led to error. The pressure methods have not only obliterated the capillary but have also disturbed the venous outflow; the hemorrhagic methods are inexact because the depth of the wound and the type of vessel severed are not known. Direct measurement by microcannulation has been the most accurate method, but clinical performance is difficult. Landis,[1] in carrying out measurements by this method, called attention to the changes in capillary pressure which occurred on raising

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nd lowering the extremity. It is these changes hich were followed in this study, using the kin color as an index of minute vessel pressure ather than capillary intubation. This method, n reality, might be called a quantitation of he old and well-tested "elevation pallor" naneuver.

The pressure in the proximal capillary and listal arteriole of the skin of the hand has been ound by direct measurement to be approximately 32 mm. Hg[1, 2] (41.4 cm. blood). The ability to produce such a pressure probably constitutes merely a pressure within a normal range since elevating the hand above the head is not followed by blanching in a normal subject and the pressure necessary to maintain this would be in the range of 50 to 75 mm. Hg (65 to 100 cm. of blood). Inversion of the body is not followed by complete blanching of the feet although the dorsalis pedis and the posterior tibial pulsations may not be palpable. Capillary pressure thus varies widely and probably also fluctuates in response to central pressure changes as measured by the auscultatory methods. It is reasonable that there must be a minimum pressure below which capillary physiology is so disturbed that failure of support of cell metabolism takes place. The filling of cutaneous vessels 41.4 cm. above heart level and the maintenance of the pink or "living" color at this height indicates the capacity of the arterial bed to develop a pressure lying within normal capillary limits, since this visible color indicates the filling of the minute vessels under which term are included the terminal arterioles, capillaries, and subpapillary venous plexus.

To secure an adequate base line for pressure measurements, we must by some means secure a release of nervous control of small vessels and dilate the minute vessels present as widely as possible. Reactive hyperemia was selected for this purpose because of its effectiveness and its simplicity of application.

The phenomenon of reactive hyperemia which follows release of temporary circulatory arrest produces a vasodilatation as great as any with the exception of muscular exercise.[5] This vasodilatation is independent of the central nervous system to a large extent and is related to the metabolic debt.[6] It affects the deep as well as the superficial circulation, the arterioles, capillaries, and venules being the main point of action.[5, 7, 8, 9] The reaction has the added advantage in a clinical sense that there is no decrease in the capacity of the small blood vessels of the skin to respond by reactive hyperemia following ischemia even in the advanced stages of obliteration of main arterial trunks.[10] Previous studies utilizing this principle of reactive hyperemia in the study of peripheral vascular diseases have been based mainly on volume flow.[10-14] Pickering's two cases of obstructive lesions of the abdominal aorta gave normal flushing times in the horizontal position following release of temporary occlusion of the circulation.[11] In this study it was felt that the pressure in the minute vessels might be of greater importance in the evaluation of peripheral vascular obliterative lesions than the volume flow.[1-4, 15, 16] Buerger apparently realized this when he attempted to evaluate circulatory failure by the use of the "angle of circulatory sufficiency."[16] The height of penetration of cutaneous hyperemia following temporary arrest of circulation was felt to be an easily available clinical measure of capillary pressure; it was understood that under certain circumstances, such as during fear, pain, or under the influence of cold, the period of reactive hyperemia would be shortened or that release of the nervous control of peripheral small blood vessel circulation would not be complete.[8, 17, 18, 19] The identification of the cutaneous hyperemia or of the normal pink color of the skin with capillary filling will be discussed in the section under methods.

Description of a New Method for Measuring Small Vessel Pressures

It was necessary to establish as valid that the appearance of the hyperemic flush or a normal pink color corresponded to capillary filling. This is not to affirm that capillaries contribute greatly to skin color, for it is already known that skin color is chiefly a reflection of filling of the subpapillary venous plexus.[20] But the filling of the meshwork of fine vessels into which they pour (collecting venules and subpapillary venous plexus) is

dependent on the blood coming through the capillaries. For this purpose, a microscope was mounted on a camera tripod so that the low-power objective could be swung into position over the elevated extremity. The nail bed of the second digit was used for observation in the lower extremity and the second or third finger in the upper extremity. The tissue at the base of the nail was carefully cleaned of any superficial debris. Mineral oil was applied to the skin at the base of the nail as a clearing agent. The intense light source was produced with a 500 watt slide projector focused through a green solution. By this method, the capillaries were easily visible and the flush of the cutaneous hyperemia was found to appear simultaneously in a given area with the filling of the capillary loops. This procedure was carried out on five individuals without evidence of peripheral vascular disease.

The blood pressure in the minute vessels of the skin of the foot has been estimated by a method of elevation and reactive hyperemia. This consists in raising the feet to 65 cm. and then applying occlusive cuffs. If on release of the cuffs reactive hyperemia does not appear, the feet are gradually lowered until flushing takes place and this level is noted. The detailed description of the method is as follows:

The patient was stabilized for a minimum of one-half hour, clothed only in a short surgical gown, in a room of moderate temperature and humidity (23 to 27 C. and a relative humidity of 40 to 60 per cent). With the patient in a supine position, the extremity to be studied was then elevated to a standard height of 65 cm. (measured from the base of the heel to the surface of the table) for a period of 10 minutes. During this period, the brachial blood pressure was noted and the skin temperature of the toes, ball of the foot, and heel was recorded. If no blanching occurred, the femoral artery was then digitally occluded and the feet emptied of blood by massage until they presented a cadaveric appearance. This ischemia was maintained by inflation of a pneumatic cuff applied at the ankle or above the knee and inflated above the systolic blood pressure (fig. 1). The occlusion was maintained for a period of five minutes if the above noted temperature was between 30 and 35 C., for 10 minutes if the temperature averaged between 20 and 30 C.[5, 8, 21, 22] On release of the occluding cuff, the height which the flush attained was measured from the surface of the table. The plantar surface of the foot was used extensively for observation since this area is subject to pressure and contact and, therefore, incurs the greatest metabolic debt and has the most

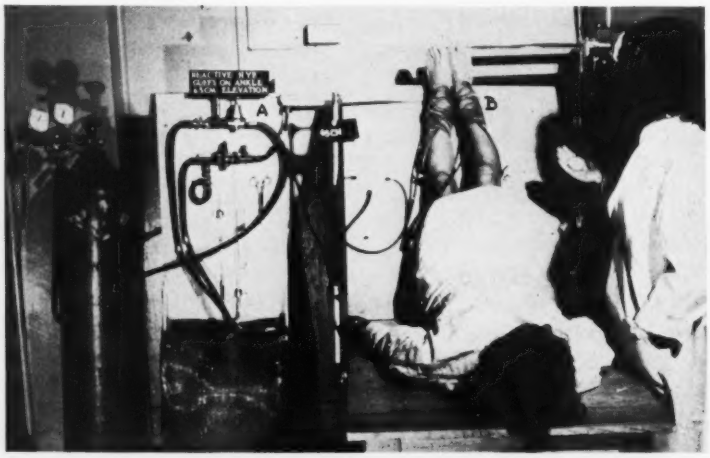

FIG. 1. Position and instrumentation for elevation and reactive hyperemia testing. (A) Reduction valves and manometer for use with commercial nitrogen tank. (B) Occlusion cuffs.

reactive blood vessels and is recipient of the most highly oxygenated blood and, hence, shows maximum color changes.[23] If a flush was not observed, the extremity was then lowered in 10 cm. decrements at 30- to 60-second intervals until a definite area of hyperemia or color was seen in the area or about the lesion under consideration. In no case was the total time for determination allowed to exceed one-half of the period of elevation or occlusion ischemia.[22] The hyperemic flare may be replaced by the appearance of a light pink or a "living" color, since, with the foot in the elevated position, the subpapillary venous plexus, which largely determines the color of the skin, is rapidly drained. In those cases in which the spontaneous and complete blanching occurred on elevation, the occlusion cuff was not used, the stimulus to reactive hyperemia being provided by a 10-minute elevation period. The phlebostatic "axis," as described by Burch and Winsor, was used as the zero point or base line.[24] For the purposes of this study the anteroposterior diameter of the chest was measured at the level of the fourth rib with an x-ray centimeter scale. One-half of this measurement was subtracted from the measured height. This height in centimeters, whether measured from the plantar surface of the foot or from an area in close proximity to a lesion elsewhere, was considered to be approximately the pressure in centimeters of blood above the right auricle necessary to fill that area. (Figure 2 shows a sample protocol.) These determinations were carried out under artificial light using a PR-1 General Electric Photoflood bulb.

Ten normal controls were observed to fill at the standard height of 65 cm. above the table in from 15 to 45 seconds. Five determinations were carried out on patients with cold, pale, wet, cyanotic feet who were considered to constitute a group with severe vasoconstrictive disease. In these cases, there was a complete filling of the sole of the foot following a release of the occluding cuff in from 15 to 45 seconds, placing them in a category with the normal controls. There was no evidence of local arterial obliteration in any patient in this group. Six observations were carried out on six patients who clearly demonstrated small vessel obliteration distal to the main arterial trunk as demonstrated by the reflex vasodilatation test, arteriography, and symptomatology. These areas could easily be mapped out during the performance of the elevation reactive hyperemia test. Complete filling was observed in all of these cases in from 15 to 45 seconds with the exception of the involved areas. These areas which blanched or exhibited pallor and subsequently filled following lowering of the part indicated a decreased or failing blood supply as compared with the rest of the foot.

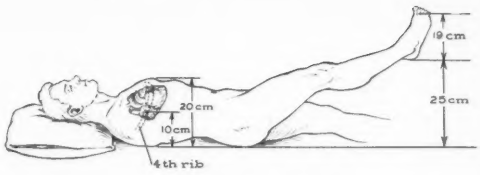

FIG. 2. Sample Protocol

Patient: M. H. (table 1, case 22). Age: 71. Blood pressure: 160/80. Length of foot: 20 cm. Chest thickness (4th rib): 20 cm. Room temperature: 25 C. Foot temperature: 22 to 27 C. No occluding cuffs used. Ten minute elevation with heels at 65 cm. above table. Heel lowered at 1.0 minute intervals to 55 cm., 45 cm., 35 cm., 25 cm.

1. Superficial necrosis of nail bed first and fourth toes left foot following therapy for dermatophytosis, also hallus valgus with pad of second toe making pressure on nail of 1st toe.

2. Numbness of toes, rest pain, and swelling of foot.

3. No response to lumbar block, foot felt subjectively better. 12-23-49, left lumbar sympathectomy.

4. Surgical Question: Can second toe be amputated with healing by primary intention?

Hyperemia noted in proximal phalanx left second toe at 25 cm., measured from table to heel.

Actual height measured from table to heel:	25 cm.
Length of foot from heel to proximal phalanx of 2nd toe:	19 cm.
	44 cm.
Height of phlebostatic axis above table:	10 cm.
Height of penetration of cutaneous hyperemia above axis:	34 cm.

Amputation, second toe, 1/16/50, followed by necrosis. Final healing by secondary intention three months later. (Height of penetration of cutaneous hyperemia at this time 50 cm.)

Application of Method to the Treatment and Prognosis of Necrotic Lesions of the Foot

A series of 90 observations was made on 78 patients. The above-noted 21 observations served as control data. The remaining 69 observations were divided as follows: 48 in patients with peripheral obliterative lesions due to arteriosclerosis; 11 in patients with arteriosclerosis and diabetes; and 10 in patients with peripheral obliterative lesions due to thromboangiitis obliterans. Of this group of 69 observations on 57 patients with peripheral obliterative arterial lesions, 26 observations were made in patients in whom amputations were carried out at the level of the forefoot or toe and 43 observations were made in patients who were treated conservatively. These cases are summarized in tables 1 and 2 with regard to their diagnoses, height of penetration of hyperemia, treatment, and result.

Discussion

In this study, relatively long periods of ischemia were used because of the observations of Scheinberg and co-workers[25] that the time necessary to produce maximal blood flow by arterial occlusion at 32 C. is much greater in the lower extremity than has been previously reported in the upper extremity. This observation is similar to the responses to intradermal histamine reported by Odgen and associates[26] demonstrating delay of response in the lower extremity as compared with the arm. Greenwood and co-workers[8] also noted that the elevated forearm required an occlusion 66 per cent longer than the horizontal forearm to produce a visible hyperemia.

Studies were carried out at a moderate temperature even though it has been demonstrated that generalized warming of the patient produces a dilatation of peripheral vessels which included an increase in muscle flow.[27, 28] The test described here was designed to be carried out at ordinary room temperatures with occlusion being provided by an ordinary sphygmomanometer cuff. Various periods of occlusion were used since metabolic demands increase with temperature[6] and the appearance of reactive hyperemia is more rapid in the warm part.[8]

The skin of the part was emptied of blood since hyperemia is more rapidly produced with the absence of residual oxygenated blood in the limb.

It will be noted in table 1 that primary union or rapid secondary healing occurred in all cases having a penetration of hyperemia above 42 cm. at the amputation level. Penetration of hyperemia 42 cm. or less was attended by failure of healing or slow union by secondary intention. These cases were selected for amputation either because conservative therapy had failed or because of destruction of the basic architecture of the part by necrosis or infection.

The cases of conservative therapy shown in table 2 were selected in most instances because of their involvement of skin and subcutaneous tissues only, because of the small area of necrosis or because of refusal of amputation by the patient. Heights of penetration of hyperemia shown are measured to the edges of the lesion. Penetrations of 33 cm. or less were attended by indolence or failure of healing with one exception. Patient G. T. (30), table 2, with a height of penetration of only 27 cm., healed in three weeks, following mechanical assistance. This study was carried out with the patient in severe pain and with a period of ischemia of only three minutes (limited by pain). Re-evaluation was refused by the patient, but simple elevation of the extremity showed maintenance of color 30 cm. above the phlebostatic "axis" at the time of discharge from the hospital.

Patient E. R., (17) table 1 and (17) (37) (40) table 2, demonstrated a gangrenous lesion which healed with partial restoration of arterial continuity and increase of pressure. A second arterial occlusion was followed by loss of pressure and re-establishment of the lesion. A more extensive thromboendarterectomy was again followed by increase in pressure and successful amputation of the part. Patient P. R., (16) (38) table 2, illustrates a similar situation. The distribution of the heights of penetration in relation to good and bad result are shown in figure 3.

TABLE 1.—*Amputation at Level of Forefoot or Toes*

Subject Age	Diagnosis and Lesion	Ht. of Hyperemia Penetration *cm.*	Treatment	Result
. S. 5 1)	Artscl. oblit.; diab.; gangrene distal phalanx 1st toes bilaterally	87+	Amp. 1st toes bilaterally	Primary union
. J.) 2)	TAO; necrosis tip rt. 1st toe; osteomyelitis of terminal phalanx	84+	Amp. rt. 1st toe	Primary union
. S. (3)	Artscl. oblit.; diab.; old traumatic amp. of right 2nd toe; necrosis and osteomyelitis of stump	79+	Amp. stump, rt. 2nd toe	Primary union
I. M. (0 (1)	Artscl. oblit.; diab.; gangrene 1st and 5th lt. toes	77+	Amp. 1st and 5th lt. toes	Primary union
A. V. 69 (5)	Artscl. oblit.; diab.; gangrene and osteomyelitis, lt. 5th toe	75+	Amp. lt. 5th toe	Primary union
A. B. 72 (6)	Artscl. oblit.; necrotic ulcer rt. 5th toe	72	Amp. rt. 5th toe	Rapid healing by 2nd intention; mobilized too early
L. B. 78 (7)	Artscl. oblit.; gangrene and osteomyelitis of distal phalanx rt. 3rd toe	65	Amp. rt. 3rd toe	Primary union
M. P. 76 (8)	Artscl. oblit.; diab.; gangrene 4th toe; tendon sheath infection	65	Toe amp. and drainage of tendon sheath followed by skin graft	Complete and rapid healing
E. P. 45 (9)	Artscl. oblit.; gangrene of lt. 3rd toe, distal phalanx	65	Amp. lt. 3rd toe, sympathectomy	Primary union
A. M. 84 (10)	Artscl. oblit.; gangrene pad of rt. 5th toe	60	Amp. rt. 5th toe	Primary union
H. M. 40 (11)	TAO; gangrene of distal one-half 3rd toe	55	Amp. toe	Primary union
T. K. 49 (12)	TAO; gangrene of distal phalanx, 3rd rt. toe accompanied by infected sinus between toes 3 and 4	50	Amp. 3rd toe, excision of sinus	Primary union
. V. 8 3)	Artscl. oblit.; diab.; gangrene of distal phalanx rt. great toe, 2nd toe, 5th toe and lateral side of foot	50	Transmetatarsal amp.	Partially primary union, part left open & rapid healing by secondary intention
. F. 2 4)	Artscl. oblit.; necrosis and osteomyelitis lt. 2nd toe following osteotomy for hammer toe	50	Amp. 2nd toe	Primary union

(*continued*)

TABLE 1.—*Continued*

Subject Age	Diagnosis and Lesion	Ht. of Hyperemia Penetration *cm.*	Treatment	Result
C. B. 44 (15)	Artscl. oblit.; irregular deformed stump	48	Revision of traumatic amp.	Primary union
J. B. 74 (16)	Artscl. oblit.; gangrene of 2nd and 3rd toes	45	Transmetatarsal amp.	Primary union
E. R. 54 (17)	Artscl. oblit.; gangrene of distal phalanx rt. 1st toe with osteomyelitis; status following thrombectomy and extensive thromboendarterectomy	45	Amp. 1st toe	Primary union
A. M. 49 (18)	TAO; persistent 0.9 cm. necrotic ulcer dorsum right 3rd toe	45	Amp. 3rd toe	Primary union
F. D. 59 (19)	TAO and artscl. oblit.; diab.; gangrene and osteomyelitis, lt. 3rd toe and forefoot to level of midshaft, 3rd metatarsal and necrotic ulcer of skin over navicular bone	43	High transmetatarsal amp. with partial closure	50% primary union; 50% secondary union; good result
C. S. 60 (20)	TAO; gangrene of entire lt. 1st toe and distal and middle phalanges of 2nd toe	42	Transmetatarsal amp. through shafts of 1st and 2nd metatarsals	Slow healing by secondary intention
W. M. 68 (21)	Artscl. oblit.; gangrene of 1st, 2nd and 3rd toes	35	Amp. of 1st, 2nd and 3rd toes	Failure of healing, aortic thrombosis, death
M. H. 71 (22)	Artscl. oblit.; infection and necrosis of nailbed lt. 1st and 4th toes, superimposition of pad of 2nd toe on nailbed of 1st toe	34	Amp. lt. 2nd toe	Failure of healing—indolent lesion. Cf. Table 2 (15) at later date
J. D. 79 (23)	Artscl. oblit.; infection and necrosis lt. 3rd toe	20	Amp. toe and revision with failure. Transmetatarsal amp.	Gradual granulation and relief of pain over period of 6 mos.
J. M. 64 (24)	TAO; gangrene right 4th and 5th toes to level of shaft of proximal phalanx	0	Amp. rt. 4th and 5th toes	Failure of union, necrosis of flaps, infection, supracondylar amputation
E. S. 77 (25)	Artscl. oblit.; diab.; gangrene of opposing areas of lt. 2nd, 3rd and 4th toes	0	Transmetatarsal amp.	Failure of primary union, gangrene of lateral ½ of both skin flaps; died 4 mos. later, cardiac failure. Cf. Table 2 (41)
H. T. 73 (26)	Artscl. oblit.; gangrene tip 1st toe beneath nailbed	0	Transmetatarsal amp.	Failure of primary union

Artscl. = arteriosclerosis obliterans; TAO = thromboangiitis obliterans; Diab. = diabetes mellitus; Amp = amputation.

TABLE 2.—*Conservative Therapy*

Subject Age	Diagnosis and Lesion	Ht. of Hyperemia Penetration *cm.*	Treatment	Result
W. C. 67 (1)	Artscl. oblit.; necrotic 2 cm. ulcer of skin over head of left 1st metatarsal following excision exostosis left 1st metatarsal	77	Limited walking, protection	Complete healing following development of collater circulation. Cf. (28)
A. V. 6[illegible] (2)	Artscl. oblit.; diab.; local areas of necrosis lt. 1st and 5th toes and rt. 1st toe	75	Oscillating bed	Complete healing
C. A. 67 (3)	Artscl. oblit.; postphlebitic leg with venous valvular insufficiency and recurrent lt. pretibial ulceration; excision and grafting on two occasions	70	Elastic compression	Complete healing
H. B. 50 (4)	TAO; 1.0 cm. necrotic ulcer rt. 1st toe	70	Oscillating bed, applicator stick debridement	Complete healing
L. M. 71 (5)	Artscl. oblit.; diab.; necrotic ulcer 0.7 cm. rt. 5th toe	67	Buerger's exercises, whiskey, protection	Complete healing
F. R. 62 (6)	Artscl. oblit.; superficial necrotic lesions of lt. heel, medial and lateral sides forefoot due to elastic bandaging	65	Elevation of head of bed, Buerger's exercises	Complete healing
E. P. 72 (7)	Artscl. oblit.; 2.5 × 4.0 cm. necrotic ulcer rt. heel with accompanying infection; eczematoid dermatitis rt. foot	65	Bed rest, sympathect.	Complete healing
S. H. 72 (8)	Artscl. oblit.; gangrenous 0.5 cm. ulcer lt. 3rd toe pad	65	Bed rest, lumbar sympathect., excision of hyperkeratotic area surrounding ulcer	Complete healing 14 days
C. F. 70 (9)	Artscl. oblit.; diab.; 1 × .5 cm. necrotic ulcer rt. 1st toe and a necrotic fissure rt. heel	65	Oscillating bed, protection	Complete healing
E. C. 83 (10)	Artscl. oblit.; necrosis (3–4 mm.) tip lt. 1st toe and surrounding area of capillary stasis	65	Thermostatic cradle, bed rest	Complete healing
M. T. 6[illegible] (11)	Artscl. oblit.; 1.0 cm. necrotic ulcer lateral aspect rt. 1st toe accompanied by osteomyelitis terminal phalanx	63	Elevation of head of bed, Buerger's exercises	Complete healing
A. M. 8[illegible] (12)	Artscl. oblit.; 1.0 cm. necrotic ulcer over rt. 1st metatarsal head	60	Oscillating bed, thermostatic cradle	Complete healing
W. B. 8[illegible] (13)	Artscl. oblit.; 0.9 cm. necrotic ulcer lt. 1st toe	58	Oscillating bed, thermostatic cradle	Complete healing

(*continued*)

TABLE 2.—*Continued*

Subject Age	Diagnosis and Lesion	Ht. of Hyperemia Penetration *cm.*	Treatment	Result
S. E. 59 (14)	Artscl. oblit.; necrotic 1.0 cm. ulcer over head of right 1st metatarsal (postbunionectomy)	55	Oscillating bed, thermostatic cradle	Complete healing
M. H. 71 (15)	Artscl. oblit.; infection and necrosis of nailbed lt. 1st and 4th toes, necrotic ulcer amputation stump lt. 2nd toe	50	Bed rest, thermostatic cradle	Complete healing. Cf. tabl 1 (22) at earlier dat
P. R. 82 (16)	Artscl. oblit.; necrotic ulcer tip lt. 2nd toe; status following thromboendarterectomy	50	Oscillating bed, protection	Complete healing. Cf. (38
E. R. 54 (17)	Artscl. oblit.; gangrene of distal phalanx rt. 1st toe with osteomyelitis; status following thromboendarterectomy	50	Oscillating bed, removal of distal phalanx (exposed bone)	Complete healing excep for sinus tract over e posed bone. Cf. (37) (40
C. B. 44 (18)	Artscl. oblit.; gangrene and infection entire rt. great toe, posttraumatic	48	Oscillating bed, sympathect.	Complete healing
F. B. 78 (19)	Artscl. oblit.; gangrene nailbed 3rd rt. toe	45	Oscillating bed, thermostatic cradle	Slow healing, one month
S. J. 70 (20)	Artscl. oblit.; gangrene and infection of tip and lateral side lt. 5th toe	45	Elevation of head of bed, bed rest, Buerger's exercises	Complete healing except for small sinus tract from osteo. of terminal phalanx
A. W. 78 (21)	Artscl. oblit.; 1 cm. gangrenous fissure rt. heel; gangrene tip rt. 1st toe; status following thromboendarterectomy	45	Oscillating bed, thermostatic heat cradle	Complete healing. Cf. (36)
G. F. 72 (22)	Artscl. oblit.; 3 cm. necrotic ulcer medial aspect lt. 1st metatarsal head	40	Elevation head of bed, Buerger's exercises, saline soaks	Complete healing
J. O. 77 (23)	Artscl. oblit.; 2 cm. necrotic lesion lt. heel	40	Protection, elevation of head of bed, lukewarm saline soaks, Buerger's exercises	Complete healing
J. H. 35 (24)	TAO; recurrent necrotic ulcer of entire nail bed of lt. 3rd toe	40	Bed rest, lumbar sympathect.	Healing original lesion slow; recurrence; more rapid healing following sympathectomy
E. M. 72 (25)	Artscl. oblit.; necrotic ulcer 3.5 cm. in diameter, rt. heel	38	Bed rest, elevation of head of bed, Buerger's exercises	Complete healing
M. S. 61 (26)	Artscl. oblit.; gangrene distal phalanx lt. 5th toe; status following thromboendarterectomy	35	Oscillating bed, protection	Complete healing. Cf. (32

TABLE 2.—*Continued*

Subject Age	Diagnosis and Lesion	Ht. of Hyperemia Penetration *cm.*	Treatment	Result
. W.) 7)	Artscl. oblit.; necrotic 0.8 cm. ulcer lt. great toe at interphalangeal junction	33	Oscillating bed, heat cradle 85–90 F.	Lesion indolent, healing required over one month
. C. 7 8)	Artscl. oblit.; necrotic 2 cm. ulcer of skin over head lt. 1st metatarsal following excision of exostosis of lt. 1st metatarsal	32	Bed rest, Buerger's exercises, protection	Failure of healing after 3 mo. treatment. Cf. (1) 14 mo. later
. H. 5 9)	Artscl. oblit.; areas of capillary stasis, tips all toes, rt. foot	30	Bed rest, Buerger's exercises, thermostatic cradle	Gradual progression, rest pain and claudication
. T. 4 0)	TAO; necrotic infected ulcer beneath rt. 1st toe nail	27	Oscillating bed, removal of toe nail, thermostatic cradle	Complete healing
F. M. 60 (31)	Artscl. oblit.; 2 cm. gangrenous lesion lt. great toe; small areas capillary stasis all other lt. toes	20	Oscillating bed, thermostatic cradle, sympathect.	Gradual progression, midthigh amputation
M. S. 61 (32)	Artscl. oblit.; gangrene distal phalanx lt. 5th toe	20	Bed rest, protection, Priscoline, Buerger's exercises	Indolent, non-healing, progressive, endarterectomy. Cf. (26)
H. M. 51 (33)	Artscl. oblit.; necrosis distal phalanx rt. 1st toe	20	Elevation of bed, Buerger's exercises, protection, lumbar sympathect.	Gradual progression, supracondylar amputation
L. M. 70 (34)	Artscl. oblit.; necrotic 0.5 cm. ulcer lt. 2nd toe; 1 cm. ulcer lt. heel	20	Elevation of head of bed, Buerger's exercises, warm saline soaks, protection	Gradual progression, supracondylar amputation
J. C. 73 (35)	Artscl. oblit.; bilateral popliteal aneurysms; gangrene tip rt. 1st toe beneath nail; 2 cm. necrotic ulcer dorsum of rt. foot	10	Oscillating bed, bed rest, protection of part	Failure of healing for over 1 mo., supracondylar amputation following attempted repair of aneurysm
A. W. 78 (36)	Artscl. oblit.; gangrene 1st rt. toe; 1.0 cm. undermined fissure rt. heel	0	Oscillating bed, thermostatic cradle, protection	Progression of lesions, endarterectomy. Cf. (21)
. R. 4 7)	Artscl. oblit.; gangrene distal phalanx rt. 1st toe with osteomyelitis	0	Oscillating bed, thermostatic cradle, protection	Progression of lesion, endarterectomy. Cf. (17) (40)
. R. 2 8)	Artscl. oblit.; necrotic ulcer tip lt. 2nd toe	0	Oscillating bed, thermostatic cradle	Progression of lesion and symptoms, endarterectomy. Cf. (16)
. B. 7 9)	Artscl. oblit.; necrotic infected ulcer beneath rt. 1st toe nail; postphlebitic ulcer rt. ankle	0	Oscillating bed, removal of nail, protection	Failure of healing, supracondylar amputation

(*continued*)

TABLE 2.—*Concluded*

Subject Age	Diagnosis and Lesion	Ht. of Hyperemia Penetration *cm.*	Treatment	Result
E. R. 54 (40)	Artscl. oblit.; gangrene distal phalanx rt. 1st toe with osteomyelitis; status following thromboendarterectomy; recur. thrombosis and partial distal phalangectomy	0	Oscillating bed, thermostatic cradle, protection	Progression of lesion, supracondylar amputation. Cf. (17) (37)
E. S. 79 (41)	Artscl. oblit.; diab.; gangrene opposing areas left 2nd, 3rd and 4th toes	0	Oscillating bed, thermostatic cradle, protection	Progression of lesions, transmetatarsal amputation. Cf. table 1 (25)
J. W. 63 (42)	Artscl. oblit.; aneurysm abdom. aorta; status following wiring of aneurysm; gangrene of dorsum rt. 2nd toe; multiple 1.0 mm. lesions dorsum rt. foot	0	Bed rest, protection	Supracondylar amputation
S. J. 42 (43)	TAO; gangrene entire 3rd toe and encroachment on dorsum of foot	0	Oscillating bed, protection	Supracondylar amputation

Artscl. oblit. = arteriosclerosis obliterans; Diab. = diabetes mellitus; TAO = thromboangitis obliterans.

Patients shown in tables 1 and 2 had been previously studied by oscillometry, arteriography, reflex vasodilatation tests, sympathetic nerve block, peripheral nerve block and biopsy as well as by general clinical and laboratory evaluation.[29] The only correlation found was that of height of penetration of hyperemia with healing of necrotic lesions and primary healing of amputations of the foot.

It is realized that adequate capillary pressure is only one factor in the healing of these lesions. Surgical study has revealed certain factors which are necessary not only for wound healing but also probably for normal tissue metabolism and maintenance of tissue viability. These requirements can be placed in the following major groupings: (1) Adequate capillary pressure; (2) effective blood osmotic pressure; (3) normal venous pressure; (4) normal lymphatic outflow; (5) adequate level of formed elements in the blood; (6) adequate blood and tissue vitamin and enzyme levels; (7) absence of infection. These factors become of greater importance in the tissue repair following trauma when inflammatory processes with local metabolic increases are necessary. These same factors must be carefully considered in any case demanding the healing of necrotic lesions of the foot or the amputation wounds resulting from the treatment of these lesions.

Therapy was generally uniform in both the conservatively handled cases and in the amputation group. It was directed toward restoring to normal the factors just considered. Elevation of the head of the bed combined with Buerger's exercises or the use of the oscillating bed was employed. Thermostatically controlled heat cradles regulated from 85 to 95 F. were used in some cases. Warm saline soaks (80 to 90 F.) were used to prevent formation of crusts and retention of secretions. Antibiotics were used in all instances and bacterial sensitivity tests were carried out in some cases. Blood transfusions and vitamins were given as required.

All amputations in this series were carried out in approximately the same manner. The skin was prepared with soap and water or hexacholorophene[30, 31] by the operating surgeon. All soft tissues were cut with a scalpel; the original incision was carried down to the bone

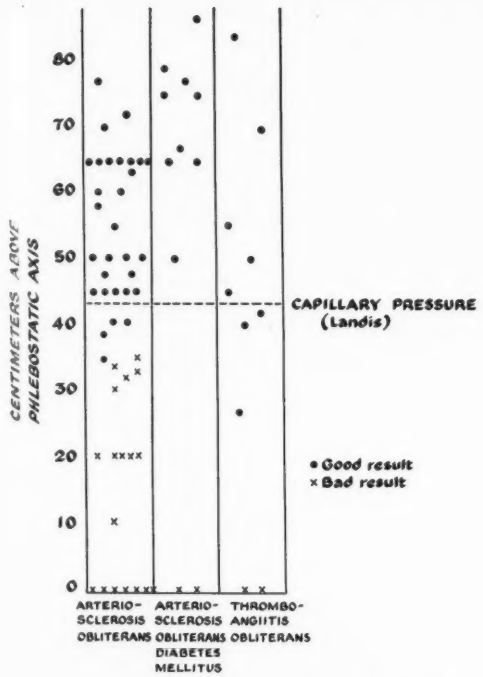

FIG. 3. Distribution of heights of penetration of cutaneous hyperemia in relation to result shown in comparison with capillary pressure (Landis) converted to centimeters of blood.

at all points. Joint spaces were avoided whenever possible. The deep fascia and equal skin flaps were closed without tension. Number 100 cotton suture material was used to close both the fascia and the skin. No thumb forceps or hemostats were used during the entire procedure. Operating lamps productive of large amounts of radiant heat were avoided, and sponges wet with cool saline were used as necessary. The part was then dressed with xeroform gauze, fluffed gauze sponges, and lightly appiled stockinette bandages cut on the bias.

SUMMARY

A simple elevation reactive hyperemia test which is useful in estimating the development of collateral circulation in obstructive peripheral vascular diseases and in separating these from vasospastic conditions has been described. The filling of the capillaries of the skin has been observed to correspond to the spread of the hyperemic flare of pink flush. The filling pressure of the minute vessels as measured by elevation and reactive hyperemia seems to vary between wide limits. The lower limit of pressures necessary to allow spontaneous healing of necrotic lesions under the conditions described seems to be in the magnitude of 35 cm. above the phlebostatic "axis." A similar limit for the successful performance of amputation at the level of the forefoot or toes seems to exist at about 45 cm. above the phlebostatic "axis."

ACKNOWLEDGMENTS

We wish to express our gratitude to Mr. Terry T. Masuda and Mr. Robert G. Givens for their assistance.

SUMARIO ESPAÑOL

Se describe la prueba de hiperemia reactiva a la sencilla elevación la cual es útil en el estimado del desarrollo de circulación colateral en enfermedades obstructivas perífero vasculares y en la separación de estas de las condiciones vasoespásticas. El henchimiento de los capilares de la piel según se ha podido observar corresponde al esparcir de la hiperemia del sonrojo. La presión de henchimiento de los vasos minutos medida por medio de elevación y hiperemia reactiva parece variar entre grandes límites. El límite más bajo de presiones necesarias para permitir la cicatrización de lesiones necróticas bajo las condiciones descritas parece ser de una magnitud de 35 cm. sobre el "eje" flebostático. Un límite similar para el buen resultado al hacer amputaciones al nivel de la pata delantera parece existir a un nivel aproximadamente de 45 cm. sobre el "eje" flebostático.

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Studies on the Effect of Exercise on Cardiovascular Function

II. The Blood Pressure and Pulse Rate

By Robert S. Fraser, M.D., and Carleton B. Chapman, M.D.

Attempts to follow changes in blood pressure induced by exercise, using indirect sphygmomanometry, have yielded conflicting results. In the following study, blood pressure measurements were made at rest (standing), during a standard treadmill work load, and during a six-minute recovery period, using a direct method and a suitably damped recording system. It was found that during exercise systolic pressure rises and that diastolic pressure falls, the net result being very little change in the mean pressure. In some subjects there is a secondary rise in all three items between 10 and 30 seconds after cessation of exercise. Changes in pulse rate during exercise and recovery are also discussed.

A NUMBER of authors have drawn attention to the difficulty of measuring the changes in blood pressure which take place immediately after the cessation of exercise in man.[1-4] It is well known that rapid fluctuations may occur in the first 15 seconds of recovery, a situation which makes measurement of blood pressure impossible by ordinary sphygmomanometric means. The error introduced by use of indirect measurement of blood pressure during and after exercise has recently been studied by Henschel and colleagues.[5] Partly because of these difficulties a number of conflicting reports have appeared, and these have been reviewed by Nielsen,[4] Simonson and Enzer[6] and Glaser.[3]

Numerous reports are available concerning changes in pressure during exercise, and it is generally agreed that systolic pressure increases. There is less agreement concerning corresponding changes in diastolic pressure. In a study on eight subjects, who bicycled at various rates, Christensen[2] found that systolic pressure increased, reaching a constant level by the end of five minutes of exercise, and that diastolic pressure also showed increases which ranged from 13 to 38 per cent depending on the rate of work. Simonson and Enger[6] stated that diastolic pressure remains constant or increases slightly during exercise; others have reported that it shows no change.[3, 7]

In spite of the difficulty in recording rapid changes in blood pressure during recovery from exercise with the mercury manometer some workers have made such observations. On the strength of such data, Barringer[8] set up criteria of normality based on the time taken by the blood pressure to return to the resting level. Bruce and colleagues[9] recorded the blood pressure in normal subjects 10 times during a nine-minute recovery period which followed a walk on a treadmill for 10 minutes at 2.6 miles per hour. They noted little change between the resting and recovery pressures, and no significant difference between responses of men and women. Stevenson and others[10] found a reduction in diastolic pressures at two, three and five minutes after cessation of exercise. Return of both systolic and diastolic pressures to pre-exercise values generally did not occur until the tenth minute of recovery although systolic pressures were close to the resting values at the fifth minute. Similar reductions in diastolic pressures have been noted by others, as reviewed by Glaser.[3] In a study of the effect of exercise on blood pressure in undernourished and subsequently well-nourished civilians in German prison camps, Glaser

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found both increases and decreases in diastolic pressure during recovery from stair climbing. He concluded that there was no diagnostic value to blood pressure measurements after exercise.

Recently, blood pressure changes during exercise have been measured intra-arterially by Eskildsen and co-workers,[1] who concluded, on the basis of 20 experiments performed with this much more exact technic, that: (1) systolic pressure rises rapidly after the start of work; (2) systolic pressure falls rapidly immediately after cessation of work, then more slowly, reaching values which are sometimes below the resting ones by the fourth or fifth minute; and (3) diastolic pressure varies little, but may follow the systolic changes on a minor scale.

Changes in pulse rate with exercise have been studied by many workers in an attempt to relate the increase in pulse rate during exercise and the time taken for it to return to resting levels, on the one hand, and the cardiac status, on the other. In normal subjects the pulse rate quickly reaches a plateau during steady work. It has been shown that the pulse rate not only increases more, but also takes longer to return to resting levels in anxious and "preoccupied" subjects than in normal ones.[10] In a small number of normal subjects, Bierring[11] found that the pulse rate increased in a linear manner with increase in work and decreased during recovery to a constant level somewhat above the resting rate. He further stated that in normal persons the pulse rate during recovery never fell below the resting rate.

Use of a treadmill to provide a standard work load, and of intra-arterial pressure recording in order to follow rapid changes in blood pressure, offers means of overcoming the difficulties encountered in some of the previous studies. The following investigation, embodying these two technical features, was undertaken in the hope of resolving some of the confusion that now exists in this important area.

Methods and Materials

Subjects were divided into three groups: 11 young women, aged 22 to 30; 19 young men, aged 18 to 39; 11 older men, aged 40 to 57 years. All subjects were in good health and gave no history of cardiovascular disease. All were fasting.

The recording system consisted of a polyethylene catheter (inside diameter, 0.58 mm.; outside diameter 0.96 mm.) connected by a 22 gauge needle, an orifice damping device (a modified 23 gauge needle), and a three-way stopcock to a Statham strain gauge (0 to 75 cm. Hg). Impulses were recorded on a Sanborn Polyviso recorder. The damping device was so adjusted that the system provided a flat frequency response to 19 cycles per second.

The catheter was inserted into the brachial artery through a thin-walled 18 gauge needle and was then connected to the other parts of the system described above. The catheter was kept filled with heparinized saline which was introduced, when necessary, from a pressure system. The resting blood pressure was recorded while the subject stood quietly on a motor-driven treadmill. The subject then walked on the treadmill at 3 miles per hour on a simulated grade of 5 per cent for 10 minutes. At the end of this time, the subject having reached a steady state, a second recording was made for 30 seconds with the exercise continuing. The treadmill was then stopped and a continuous record was made for one minute after cessation of exercise. Recordings were made for the first 20 seconds of each subsequent minute for a total of five minutes.

Each blood pressure tracing was calibrated by introducing known pressures with a mercury manometer. Systolic and diastolic pressures were measured, covering one or more respiratory cycles, in each portion of the tracing except that taken during the first minute of recovery. Complexes recorded during that time were measured throughout each five-second interval for the first 30 seconds and each 10-second interval for the second 30 seconds.

Mean pressures were obtained by electric integration and recorded on a second channel at the same time that the pulse contour tracing was being recorded. Comparison of mean pressures obtained by electric, with those obtained by planimetric, integration showed that both methods gave substantially the same result.

Discussion

Blood pressure changes during exercise and recovery for each of the groups of subjects, expressed as per cent change from resting values, are shown in figures 1, 2, and 3. Values for the fourth, fifth, and sixth minutes did not differ significantly from those recorded at the beginning of the third minute and are not included in these figures. The average absolute blood pressures are given in table 1. Continuous pressure recordings were obtained

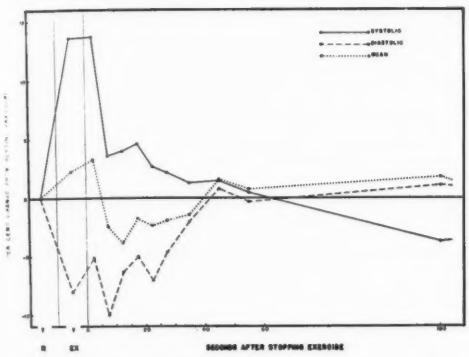

FIG. 1. Per cent changes from resting values of systolic, diastolic and mean blood pressures during exercise and during a six-minute recovery period in seven men, aged 18 to 39. R, resting blood pressure; Ex, blood pressure during exercise.

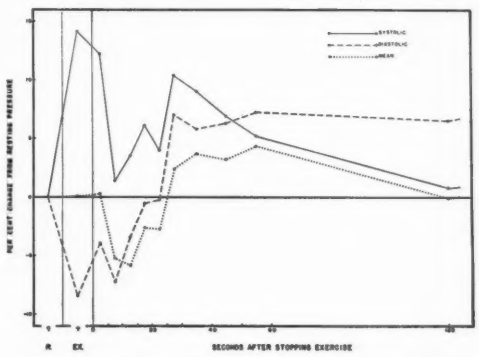

FIG. 2. Per cent changes from resting values of systolic, diastolic and mean blood pressures during exercise and during a six-minute recovery period in 11 men, aged 40 to 57. R, resting blood pressure; Ex, blood pressure during exercise.

throughout the first minute of recovery in only seven of the group of younger men (fig. 1); pressures during exercise and at the beginning of each minute, after the first minute, were obtained for all 19 young men, and the mean values for the whole group for those times do not differ from the mean values for the seven subjects (which are used in the construction of fig. 1).

Changes during exercise were similar in each group. There was a rise in systolic pressure and a fall in diastolic pressure. Both changes were statistically significant. The mean pressure showed little change from resting values in any group.

During the first minute of recovery in both the younger and older men there was an immediate and significant fall in systolic pressure by the 6 to 10-second point. In contrast the systolic pressure in the young women fell gradually until the end of the first minute. A second significant rise in systolic pressure occurred between 10 and 30 seconds in the older men but not in the younger men.

In each of the three groups the diastolic pressure slowly rose and by the end of the first minute had risen to the resting level or exceeded it. In the group of older men the rise above the resting level attained statistical significance.

The mean pressure fell to a statistically significant degree during the first 10 seconds of

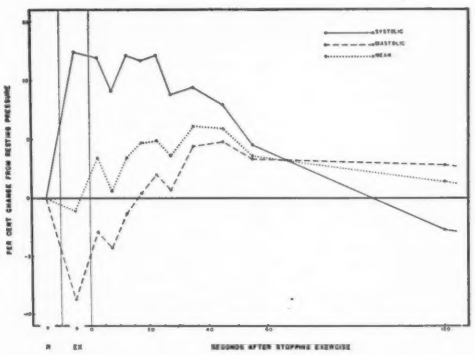

FIG. 3. Per cent changes from resting values of systolic, diastolic and mean blood pressures during exercise and during a six-minute recovery period in 10 women, aged 22 to 30. R, resting blood pressure; Ex, blood pressure during exercise.

recovery in both the younger and older men. There was no significant change in mean pressure during this time in the young women, but a significant increase in mean pressure occurred between 10 and 50 seconds in both the young women and older men.

By the beginning of the sixth minute the systolic pressure was practically the same as the resting value in the older men and only slightly less than the resting values in the younger men and young women; in each group the diastolic pressure exceeded the resting value at this point. The mean pressures in each

TABLE 1.—*Average Systolic, Diastolic, and Mean Blood Pressures in Normal Subjects at Rest, during and after Exercise*

		Rest	Exercise	Seconds after exercise							Minutes after exercise				
				0–5	6–10	11–15	16–20	21–25	26–30	31–40	41–50	51–60	3	4	
Younger men	Syst. mean	117.8	132.4	133.8	123.4	125.0	122.8	121.5	120.6	119.5	120.1	118.7	115.5	114.8	11 .4
	SD	10	19	10	18	14	12	24	8	15	12	7	9	10	2
	Diast. mean	74.2	67.0	71.2	68.6	71.6	70.1	69.4	70.7	73.3	75.7	75.0	76.4	75.5	7 .7
	SD	11	11	12	8	9	10	11	6	10	4	8	10	16	2
	Mean mean	90.9	89.3	91.3	87.5	87.8	89.1	89.5	90.1	91.2	94.0	93.6	91.3	88.0	8 .6
	SD	8	15	15	7	12	14	7	14	13	12	9	9	14	1
Older men	Syst. mean	123.4	141.5	139.2	125.9	128.5	131.4	129.0	136.7	134.9	132.2	130.5	124.2	123.3	12 .4
	SD	17	17	18	20	21	20	19	19	16	14	17	13	11	1
	Diast. mean	76.1	69.4	72.9	70.4	73.1	75.5	75.6	81.0	80.0	80.6	81.1	80.8	81.9	8 .2
	SD	9	6	8	7	6	8	9	8	7	7	6	7	6	
	Mean mean	94.8	94.7	95.0	89.8	89.0	92.0	91.9	96.6	97.9	97.5	98.5	94.6	95.6	9 .5
	SD	13	11	11	9	11	11	13	12	9	10	9	10	9	1
Young women	Syst. mean	115.5	128.6	130.1	127.1	130.4	130.2	130.6	126.7	127.4	125.6	122.8	121.8	110.0	107 .1
	SD	9	12	13	14	16	15	8	11	9	12	10	9	8	7
	Diast. mean	71.5	64.4	70.1	69.2	71.4	72.8	73.8	72.8	75.5	75.8	75.0	73.6	73.1	7 .1
	SD	5	7	9	7	10	6	7	5	5	5	5	4	5	6
	Mean mean	87.5	86.1	91.4	89.2	91.6	92.9	93.0	91.8	93.9	93.9	92.5	88.2	85.7	8 .5
	SD	6	8	14	10	8	8	10	7	8	6	6	6	7	7

group closely approached the resting value.

Considerable variation was noted in the pattern of blood pressure response in individual subjects. The most consistent change was a rise in systolic pressure during exercise which occurred in all but two subjects; the next most consistent item was a fall in diastolic pressure at the same time (37 of 41 subjects). Other changes varied more between individuals. In two male subjects, 27 and 45 years old, the systolic, diastolic and mean pressures all fell below their respective resting values for the whole period of recovery. In the man aged 45 even the exercise values were less than the resting ones.

It has been suggested in the past that satisfactory mean pressures can be calculated by halving the sum of the diastolic and systolic pressures. It is apparent from the blood pressure graphs presented (figs. 1, 2, and 3) that this method provides misleading values. At one point, the per cent change for mean pressure exceeds both diastolic and systolic per cent changes, and at other points it shows less change than either. This observation indicates that the mean pressure does not bear a fixed relationship to the systolic and diastolic pressures under changing conditions of exercise. Examination of blood pressure tracings from these subjects revealed well-marked changes from time to time in the contour of the pulse pressure waves, and the broader the pressure wave becomes (the systolic and diastolic remaining unchanged), the higher the true mean pressure. This change in mean pressure passes unnoticed if only the systolic and diastolic pressures are used for the calculation. It thus becomes obvious that the true mean pressure is not synonymous with the average pressure and, indeed, bears no fixed relationship to it under varying hemodynamic conditions.

The average increase in pulse rate during and after exercise followed much the same pattern in each of the groups. In the women there was a secondary increase in pulse rate recorded at the beginning of the third and fourth minutes after exercise, but at six minutes the average rates in all three groups were 15 to 23 per cent above resting values. The latter observation confirms Bierring's finding in normal subjects.[11]

We interpret these changes to mean that exercise induces a net decrease in peripheral

esistance as well as an increase in cardiac utput, measurements of which have recently een reported. Presumably the vascular bed n the voluntary muscles is enormously exanded, while that in other regions, such as he splanchnic area, is unchanged or even onstricted. The net result is that mean arerial pressure changes vary little, since the lterations in systolic and diastolic pressures re opposite in direction. The physiologic ignificance of the pressure changes during ecovery are poorly understood but undoubtedly complex. The possibility that the secondary, or "rebound," rise in pressure early in recovery in the male subjects may have special diagnostic significance was not investigated. Any project of this sort must take into account the fact that such a secondary rise is frequently seen in normal men and that the degree of secondary rise varies considerably from individual to individual.

Conclusions

1. During exercise in normal subjects the systolic pressure rises, the diastolic pressure falls, and the mean pressure does not change significantly when measured by a direct intra-arterial method.

2. In men, during the first few seconds after cessation of exercise, the systolic pressure falls precipitously, the diastolic pressure changes little, and the mean tends to fall. In women, the systolic pressure falls more gradually than in the men, but the validity and the significance of this sex difference are uncertain.

3. Between 10 and 30 seconds after cessation of exercise, the older men show a significant secondary rise in all three pressure items. Younger men and women fail to show a secondary rise in systolic pressure but demonstrate a gradual increase in both diastolic and mean pressures.

4. By the beginning of the sixth minute of recovery from exercise, the mean pressure returns to, or nearly to, the resting level in all three groups of subjects. Systolic pressure is close to, or slightly less than, the resting value, and the diastolic pressure in each group remains somewhat above the resting level.

5. Changes in pulse rate during and after exercise are similar in all three groups. By the sixth minute after exercise pulse rates in each group still exceed the respective resting values by about 15 per cent.

Sumario Español

Atentados a observar los cambios en presión arterial inducidos por el ejercicio usando esfigmomanometría indirecta ha producido resultados controversiales. En el siguiente estudio, las presiones arteriales fueron determinadas durante el descanso (parado), durante una caminata standard en el molino de rueda de andar, y durante un período de recuperación de seis minutos, usando un método directo y un sistema registrador convenientemente apagado. Se encontró que la presión sistólica aumenta y la diastólica disminuyó el resultado neto siendo un cambió muy Pequeño en la presión promedio. En algunos sujetos hay una elevación secundaria en los tres ítems entre 10 y 30 segundos luego de el cese e ejercicio. Cambios en la frecuencia del pulso durante el ejercicio y la recuperación también se discuten.

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Metabolic Changes Associated with Mitral Valvuloplasty

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Patients with chronic congestive heart failure operated upon for the surgical correction of mitral stenosis have been observed repeatedly to have low plasma sodium concentrations and elevated plasma potassium concentrations after operation. This study was primarily directed at an understanding of these abnormalities. The authors have shown that the preoperative patient has a characteristic disorder of body composition noteworthy for a high total body water, a high total body sodium, a low total exchangeable potassium and a low plasma sodium concentration. The effects of surgery on this abnormal body composition, and the therapeutic implications are discussed.

DURING recent years increasing attention has been paid to the metabolic response to a wide variety of surgical operations.[1] It has been shown that many factors influence this response. Of these, the previous health and nutritional state of the patient, and the severity of the inflicted trauma, are probably the most important. Coincidentally with these studies, technics have been developed for investigating the total amounts of water, sodium and potassium in the body available for exchange with suitable isotopes.[2–5] Already some knowledge of the amounts of these substances present in normal individuals has been gained and is available for comparison with the measurements made in patients before and after surgical operations.[6, 7]

By combining the balance and isotope dilution technics a detailed study may be made of some of the biochemical changes arising after major surgery. It is important to emphasize the dynamic character of these changes; isolated observations reveal only a static disorder, while sequential observations by these methods reveal the rapidly changing picture as each day passes. These methods are particularly valuable in investigating the complex problems that are seen after operations on the mitral valve.

In patients with mitral stenosis of such severity as to warrant surgical intervention, abnormalities in the metabolism of water and electrolytes are already present and the nutritional state has frequently considerably deteriorated as the result of longstanding heart failure. The stress of operation is then superimposed, and it is not surprising that in the postoperative period gross biochemical disturbances may become apparent. The present study is an attempt to elucidate the nature and mechanisms of some of these disturbances.

Methods and Material

The metabolic balance studies were carried out following the principles described by Moore and Ball.[1] The intake of sodium, potassium and nitrogen in the diet has been calculated from food analyses carried out in this laboratory. The intravenous intake given therapeutically or for the performance of various investigations has also been measured. In the case of blood transfusions, which were frequently large, only the readily available nitrogen, sodium and potassium in the plasma have been entered in the balance chart. Similarly only the plasma fractions of these constituents in the operative blood loss have been entered. The total amount of whole blood transfusions and blood loss have been indicated, however, in the legends of the charts. In calculating the total excretion, account has been taken of loss in the urine, feces, wound exudate and fluid drained from the chest.

The method of charting the metabolic balance is essentially that described by Moore and Ball.[1]

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The intake is charted upwards from the zero line and the output downwards from the top of the intake line. A positive balance is indicated by a shaded area above the zero line, a negative balance by an area below the zero line and enclosed by heavy lines.

The body content of water, sodium and potassium has been measured by dilution of deuterium oxide, sodium[24] (Na^{24}) and potassium[42] (K^{42}). The details, accuracy and reproducibility of these technics have been described previously.[2, b, 8] The measurements of total exchangeable sodium and potassium have, for the most part, been carried out simultaneously.[9]

The chemical methods used in the metabolic balance studies have been previously described.[1] Urinary excretion of 17-ketosteroids was measured by the method of Talbot[10] and of 17-hydroxycorticoids by the method of Reddy, Jenkins, and Thorn.[11]

Clinical Details

The study is based essentially on the investigations of three patients by metabolic balances (cases 1, 2, and 3) and on isotope dilution measurements made at intervals on these and nine other patients (cases 4 through 12). In case 12 only preoperative measurements were available as the patient died shortly after operation from cerebral embolism. The clinical details are mentioned in the text where applicable. In addition, studies of water metabolism and changes in blood chemistry as a result of operation have been carried out in an additional 81 patients. All were relatively severe cases of mitral stenosis falling into groups III and IV.[12] Mitral stenosis was the predominant lesion in all. In some, minor degrees of aortic and mitral incompetence were also present. Except for one of the balance patients (case 1) all have been studied during the relatively cool period of the year from October to March. The patients were brought into the best possible condition for surgery by medical treatment with digitalis, mercurial diuretics and low salt diets before the preliminary preoperative measurements were made. Blood transfusions were given liberally in an attempt to cover the loss at operation and later. The volume of these transfusions and of the other fluids given to the patients immediately after operation was changed at definite intervals. The nature and effects of these alterations in treatment policy will be described later. During the immediate pre- and postoperative periods the dietary sodium intake was restricted to approximately 9 mEq. a day except in cases 1 and 2 where the intake was larger, as described in the metabolic balance studies.

General Metabolic Changes

The general metabolic course of patients undergoing mitral valvuloplasty is best illustrated by the balance studies. Cases 1, 2, and 3 are accordingly described briefly in this section; certain aspects are discussed later in greater detail in the next sections along with the findings in the larger groups.

Case 1 (fig. 1 *A*, *B*, *C*). The patient, a woman 45 years of age, underwent operation May 19, 1952. She had rheumatic fever at the age of 12; at the age of 35 she suffered a right hemiplegia, apparently embolic in origin. In the ensuing 10 years her course was one of gradual deterioration; digitalis, diuretics and sodium restriction were employed. Dyspnea, orthopnea and ankle edema followed; she was fibrillating on admission and showed marked enlargement of liver and spleen, with wasting of the body. Her peripheral edema had disappeared when the study was begun. Clinical and radiologic signs of mitral stenosis were typical. Operation was technically satisfactory and convalescence uneventful save for a small pulmonary embolus on the sixteenth postoperative day. She was readmitted for follow-up study four months later (Sept. 23, 1952) at which time her exercise tolerance was vastly improved; there was no further orthopnea. She was still fibrillating; liver and spleen were still enlarged.

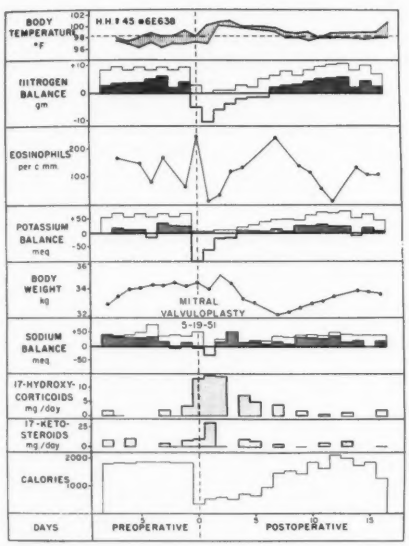
The balance of nitrogen demonstrated a transient negative phase with high excretion on one day and a rapid return to positive balance as her intake improved with resumption of caloric intake. Potassium followed a similar pattern. Sodium intake was restricted throughout, but the balance was consistently positive except for the first day after operation. Body weight showed an increase for three days postoperatively, then a sharp reduction followed by a later rise. Eosinophile count was near zero for two days after operation, then returned sharply to normal or above normal values save for two days immediately preceding her pulmonary embolus. Urinary steroid analyses showed elevation of the 17-ketosteroids on the first postoperative day; there was an increase in 17-hydroxycorticoids persisting three days and then falling slowly to the subnormal starting values.

Intake-output fluid balance (fig. 1*C*) was not remarkable; the initial total body water and total exchangeable sodium were elevated; the total exchangeable potassium was slightly low. Following operation, body water and sodium further increased as potassium decreased. On late follow-up (128 days), a return of total body water to the lowest recorded fraction of body weight (55.4 per cent) was accompanied by a fall in total exchangeable sodium and a rise in total exchangeable potassium.

The serum concentrations of sodium and potassium showed changes in opposite directions, the sodium falling and potassium rising postoperatively, and later returning towards normal. Both were normal initially.

Case 2 (fig. 2 *A*, *B*, *C*). The patient, a 40 year old woman, was operated upon Oct. 31, 1951. With no previous history of rheumatic fever, this patient was first told that she had a cardiac murmur in 1948. Within a year she noted increasing dyspnea and palpitation, and was digitalized. In 1950 she had a cerebral embolus, with left hemiplegia and gradual recovery. Disability increased although she maintained her occupation as a typist; digitalis, ammonium chloride and diuretics were used. She was thin and emaciated with a residual left-sided weakness. Typical signs of mitral stenosis were present with hepatomegaly, and cardiac enlargement. Operation was technically satisfactory; convalescence was uneventful. Her first readmission for follow-up was on Feb. 10, 1952, 105 days after operation. There was no edema. Exercise tolerance was greatly improved. Cardiac signs were unchanged. She was again studied on Oct. 31, 1952 (365 days after operation). There was still further conspicuous improvement. She was leading a normal life, symptom-free on digitalis.

Balance of nitrogen was consistently positive; there was no increase in excretion rate after operation. Potassium balance was close to zero save for a considerable period after surgery. Sodium balance showed a positive trend save for a spontaneous diuresis beginning on the fifth postoperative day,



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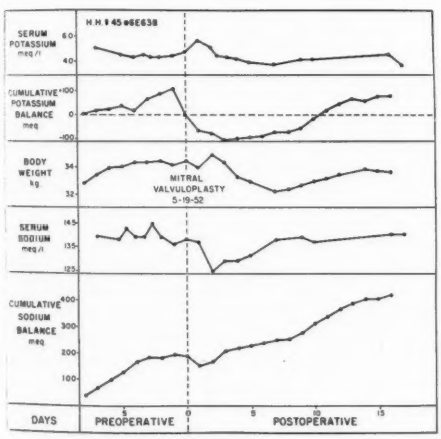

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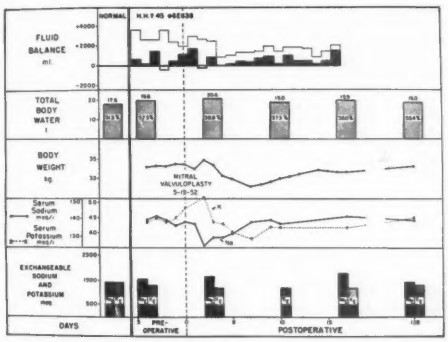

C

FIG. 1 (*A*) Case 1. Metabolic balance chart. In this and in figures 2*A* and 3 the balances of nitrogen, potassium and sodium are charted as previously described.[1] Body temperature indicates the maximum and minimum for each day. Eosinophils, body weight, caloric intake and 24-hour excretions of 17-hydroxycorticoids and 17-ketosteroids are shown. The operative blood loss was 240 ml., and blood transfusion at operation was 500 ml.

(*B*) Case 1. Cumulative balances and serum electrolyte changes. Here and in figures 2*B* and 4 each day's balance of potassium and sodium is added to the previous figure and the resultant cumulative net change charted.

(*C*) Case 1. The fluid balance is charted as in the other balances, measurable output is subtracted from total intake; in normal individuals this "intake-output balance" shows a net positive figure (+750 ml.) which represents the sum of other unmeasured losses. Total body water is charted as a column at the top of which the absolute figure (in liters) is shown. In the center of the column the water fraction of body weight is indicated as per cent. Total exchangeable sodium and total exchangeable potassium are charted as columns, the height of which represents the absolute figure as shown on the ordinate. At the left of the double line are shown normal values for body water, total exchangeable sodium and total exchangeable potassium for a female of this body weight.

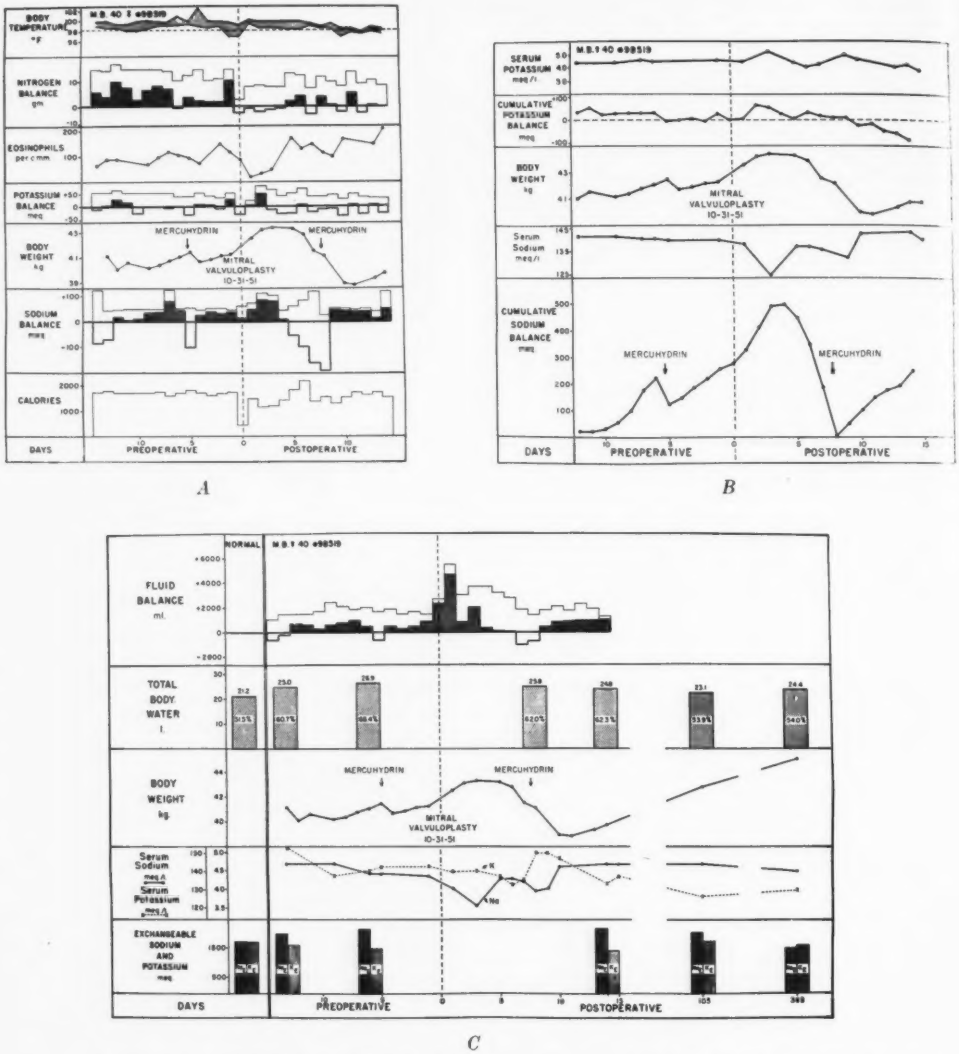

FIG. 2. (*A*) Case 2. Metabolic balance chart. The operative blood loss was 225 ml. and the blood transfusion at operation 500 ml. Further details are described in the text. (*B*) Case 2. Cumulative balances and serum electrolyte changes. (*C*) Case 2. Changes in fluid balance, body composition and serum electrolytes.

lasting four days, accounting for 500 mEq. of sodium, and towards the end of which Mercuhydrin was administered. Following this episode excretion rates again became very small. There had previously been (five days before operation) a one-day sodium diuresis (100 mEq.) on Mercuhydrin. Body weight changes followed the sodium balance; there was again in this case a postoperative weight gain, dropping abruptly during diuresis, and then rising slowly during the ensuing year. Eosinophil count was moderately low (75 to 125 cu. mm.) until operation when it dropped to near zero for three days, and then rose to values higher than those seen preoperatively. Caloric intake was never seriously impaired. Urinary steroids were not measured.

Intake-output fluid balance showed the postoperative water loading with large fluid intakes,

and later diuresis. The starting total body water and total exchangeable sodium were elevated; the total exchangeable potassium was low. These measurements were not repeated until after her diuresis and from that time a gradual and consistent approach of all these measurements toward normal was seen.

The serum concentration of sodium was initially near normal and fell abruptly to 125 mEq. per liter during the postoperative period of water and salt loading; there was then a rise and later a small dip at the very end of diuresis; only at this later time did potassium rise. These values were later normal.

Case 3 (figs. 3, 4 and 5). This patient, a woman aged 50 years, was operated upon Nov. 29, 1952. She recalled having had chorea in childhood; at the age of 15 she noticed dyspnea and palpitation on exertion; these symptoms gradually progressed. At the ages of 22 and 24 she had two normal pregnancies, and was adjusted well to her disease until the age of 42 when orthopnea and paroxysmal nocturnal dyspnea began. During the 18 months prior to admission there was rapid deterioration so that walking on the level was difficult despite digitalis and a low salt diet. She was a thin, slightly wasted woman, without edema. Auricular fibrillation, enlarged heart and liver and murmurs both systolic and diastolic were present. Operation was technically satisfactory. There was a six-day febrile period after operation during which the patient was anorexic; thereafter improvement was uninterrupted although her appetite remained poor. She was readmitted June 19, 1953 (156 days later), for

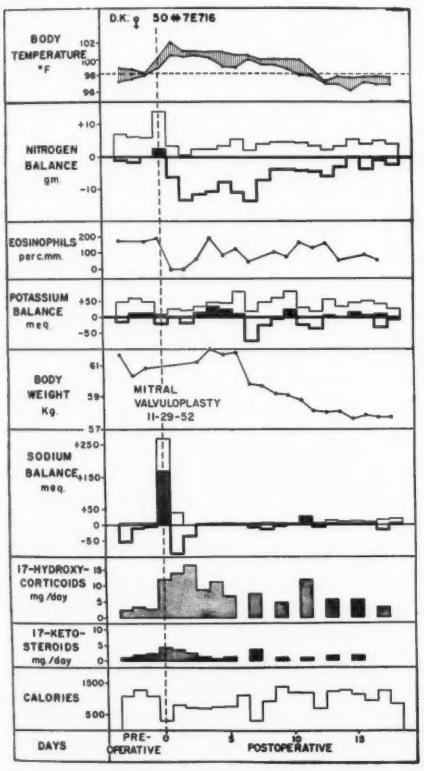

FIG. 3. Case 3. Metabolic balance chart. The operative blood loss was 334 ml. and the blood transfusion at operation 2500 ml. Further details are described in the text.

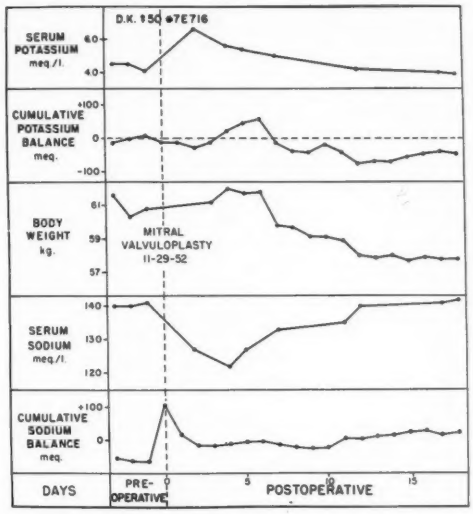

FIG. 4. Case 3. Cumulative balances and serum electrolyte changes.

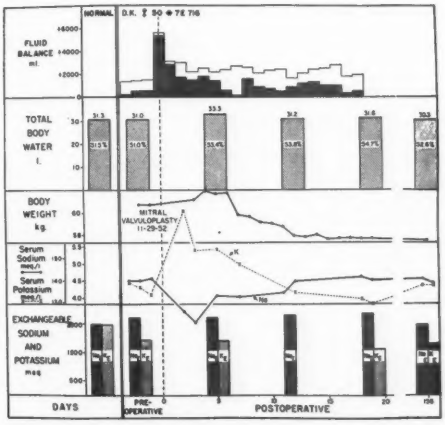

FIG. 5. Case 3. Changes in fluid balances, body composition and serum electrolytes.

study. Exercise tolerance was tremendously improved and she was leading a normal life. She had not regained her preoperative weight and was anorexic, possibly because of digitalis overdosage; cardiac signs were unchanged.

Balance of nitrogen demonstrated a marked increase in excretion rate, low intake, relative caloric starvation and marked negative balance for eight days after operation. Thereafter, excretion was less marked but balance was still negative up to discharge; daily caloric intake rarely exceeded 1000. Potassium balance was essentially zero for the duration of study. Sodium balance was a spectacular example of conservation with zero intake. Save for the day of operation when blood transfusions increased sodium intake and the following day when some sodium was lost through drainage from the chest there was a remarkable lack of sodium intake or loss. For a period of 16 days there was a total of only 160 mEq. flux with the environment, and net zero balance. Body weight rose in the early postoperative period, then fell suddenly with a large water, nitrogen and potassium loss. Thereafter, it slowly declined during the period of observation. Eosinophile count showed an operative fall. It did not at any time thereafter rise to high levels. Urinary steroid analyses showed a slight rise in 17-ketosteroid excretion over the otherwise abnormally low levels. The 17-hydroxycorticoid excretion was greatly increased for six days and intermittently elevated for eight more days.

Intake-output fluid balance (fig. 5) showed water loading for six days after operation, then a diuresis for two days, followed by normal balance. The initial total body water was not elevated, but on the fifth postoperative day it was increased by 2.3 liters, which was later excreted in the urine. At follow-up five months after operation the total body water was within the normal range. Total exchangeable sodium was elevated at the outset, and remained about the same until follow-up when it was reduced to normal. The total exchangeable potassium was low throughout.

The serum concentrations of sodium and potassium showed the conspicuous "diamond-shaped" configuration of inverse changes seen previously. The sodium, initially normal, fell to 122 mEq. per liter. This change was maximal by the second and third postoperative day, later returning to normal values.

In summary it is apparent from the metabolic studies that the response with regard to nitrogen balance, eosinophile counts and urinary steroid excretion is not beyond the range of expectation for surgical operations of similar severity.[1, 25] On the other hand, there are conspicuous abnormalities in body composition before operation and considerable disturbances in salt and water metabolism in the early postoperative period. The tendency towards lowering of the plasma sodium concentration is truly remarkable; it is often accompanied by an elevation of the plasma potassium concentration. This disorder has been the source of considerable difficulty in treatment and speculation as to pathogenesis. While a lowering of the plasma sodium concentration during positive sodium balance is a normal feature of post-traumatic metabolism (the "sodium paradox"), it does not usually occur to such a marked extent and is ordinarily not accompanied by such a marked hyperkaliemia. These aspects have accordingly been studied in greater detail in a larger group of patients.

Preoperative Body Composition

The clinical study of body composition has been greatly extended by the development of the isotope dilution methods.[7, 8] The measurement of total body water,[2, 6, 20] total exchangeable sodium and potassium[3, 4, 5, 9, 15, 17] permit the observer a remarkable insight into body composition as regards four of its most significant parameters: water, extracellular "mass" (sodium), lean tissue mass (potassium) and fat (by inverse proportion to water content).

Measurements of total body water, exchangeable potassium and exchangeable sodium were made in 12 patients before and at intervals after operation. The results are shown in table 1. In all cases except case 12 there was no peripheral edema at the time of the first measurements. The results in the female patients before operation are compared with those obtained in healthy adults in table 2. The mitral stenosis patients have a definite excess of total water and sodium in their body composition. The total exchangeable potassium is slightly diminished, but this decrease only attains a low degree of significance by statistical comparison. In case 6 no preoperative determination of total potassium was made. Only three male patients with mitral stenosis were studied with isotopes, and in them the changes in body composition were similar to those seen in the females, but the group is too small for detailed statistical analysis. The total exchange-

TABLE 1.—*Isotope Dilution Measurements before and after Mitral Valvuloplasty*

Case No.	Sex	Age Yrs.	Days before (−) or after (+) operation	Weight Kg.	Sodium			Potassium			Body Water		Fluid Intake
					Serum mEq./L.	Exchangeable		Serum mEq./L.	Exchangeable		L.	% Body Weight	
						mEq.	mEq./Kg.		mEq.	mEq./Kg.			
1	F	45	−4	34.2	139	1542	45.0	4.4	1259	36.8	19.6	57.5	Unrestricted
			+3	34.6	130	1645	47.6	4.4	1154	33.4	20.6	58.9	
			+10	33.0	137	—	—	4.2	1174	35.7	19.0	57.3	
			+17	33.7	141	1750	51.8	4.2	1169	34.6	19.9	59.0	
			+128	34.78	139	1423	41.5	4.5	1292	37.7	19.0	55.4	
2	F	40	−13	41.2	143	1932	46.9	5.1	1565	38.0	25.0	60.7	Unrestricted
			−6	41.1	139	2085	50.8	4.5	1488	36.2	26.9	65.4	
			+8	41.2	132	—	—	5.0	—	—	25.8	62.0	
			+14	39.8	143	2130	53.5	4.3	1424	35.8	24.8	62.3	
			+105	42.9	143	2018	47.0	3.9	1716	40.1	23.1	53.9	
			+365	45.20	140	1500	42.7	4.0	1564	34.6	24.4	54.0	
3	F	50	−2	60.75	140	2695	44.4	4.3	1965	32.3	31.0	51.0	Unrestricted
			+5	61.70	127	2717	44.0	5.4	1930	31.3	33.3	53.4	
			+12	58.05	140	2782	47.9	4.2	—	—	31.2	53.8	
			+19	57.78	141	2884	49.9	3.9	1628	28.1	31.6	54.7	
			+154	57.62	140	2487	43.2	4.4	1781	30.9	30.3	52.6	
4	F	22	−7	45.68	134	2144	47.2	4.3	1624	35.6	25.3	55.3	Unrestricted
			+6	46.05	129	2206	47.9	4.7	1594	34.6	29.0	64.3	
			+13	44.30	139	2328	50.4	4.4	—	—	26.0	58.7	
			+174	49.91	141	2181	43.7	4.2	2186	43.8	28.9	57.9	
5	F	47	−1	47.30	135	1985	42.0	4.0	1581	33.4	25.1	53.1	Unrestricted
			+1	48.98	124	—	—	6.1	—	—	28.1	57.4	
			+7	46.40	132	2040	43.9	4.7	—	—	—	—	
			+14	45.98	136	2125	46.2	5.0	1561	34.0	25.2	54.8	
			+167	50.69	136	2039	40.2	4.6	1914	37.8	26.6	52.5	
6	F	54	−6	45.80	137	2040	44.5	4.7	—	—	24.1	52.5	Unrestricted
			+1	46.11	130	2143	46.5	4.7	1684	36.5	26.1	55.8	
			+9	44.45	137	2086	46.9	4.7	1555	35.0	24.4	54.9	
			+15	43.92	137	2066	47.0	4.3	1418	32.3	23.4	53.3	
			+155	38.75	133	1917	49.5	4.8	1467	37.9	23.3	60.1	
7	F	40	−5	51.00	140	2127	41.7	4.9	1919	37.6	26.9	52.9	Restricted to 1500 ml.
			+2	49.10	134	2033	41.4	4.9	1728	35.2	25.9	52.7	
			+9	48.78	136	1978	40.6	4.4	1884	38.6	26.4	54.5	
			+120	51.52	143	2111	41.0	4.5	1923	37.3	26.3	51.1	
8	F	41	−1	47.05	133	1575	33.5	5.5	1600	34.0	21.5	45.7	Restricted to 1500 ml.
			+2	47.50	126	—	—	6.0	—	—	21.7	45.7	
			+7	46.35	126	1653	35.7	4.9	1317	28.4	22.5	48.5	
			+14	44.80	138	1855	41.3	4.4	1461	32.6	23.4	52.2	
			+118	57.30	140	1915	33.4	4.8	1730	30.2	23.4	40.8	
9	F	50	−7	44.70	140	2219	49.6	4.3	1658	37.1	24.8	55.4	Restricted to 1500 ml.
			−2	44.00	—	—	—	—	—	—	25.0	56.9	
			+2	42.60	126	—	—	5.3	—	—	23.6	55.4	
			+7	41.25	130	1871	45.4	5.0	1396	33.8	23.6	56.5	
			+14	41.40	135	1955	47.2	5.0	1468	35.5	23.3	56.8	

TABLE 1.—*Continued*

Case No.	Sex	Age Yrs.	Days before (−) or after (+) operation	Weight Kg.	Sodium			Potassium			Body Water		Fluid Intake
					Serum mEq./L.	Exchangeable		Serum mEq./L.	Exchangeable		L.	% Body Weight	
						mEq.	mEq./Kg.		mEq.	mEq./Kg.			
10	M	32	−2	58.60	137	2774	47.3	4.4	2829	48.3	35.2	60.1	Restricted to 1500 ml.
			+5	57.00	131	2655	46.6	5.0	2707	47.5	36.8	64.6	
			+12	56.02	138	2827	50.5	4.7	2336	41.7	35.8	65.2	
11	M	42	−11	38.62	134	2507	64.9	5.0	1645	42.6	26.1	67.6	Unrestricted
			−4	39.70	126	2501	64.6	5.0	—	—	29.4	74.7	Restricted to 1000 ml.
			+3	36.88	131	2462	66.5	5.0	1311	35.4	26.3	71.1	Restricted to 1500 ml.
			+10	36.08	133	2415	66.9	4.2	1395	38.7	—	—	
			+17	37.12	138	2595	69.9	3.8	1290	34.7	26.8	72.2	Unrestricted
			+38	39.00	139	2691	69.0	4.6	1540	39.5	27.4	70.3	
			+114	49.12	143	2643	53.8	4.3	2097	42.7	30.3	61.6	
12	M	44	−5	57.60	135	3245	57.6	4.6	2090	37.0	36.6	64.8	Unrestricted

able sodium on a milliequivalent per kilogram basis was exceptionally high in cases 11 and 12. No peripheral edema was present in case 11, but this patient was emaciated. In case 12 the high total sodium was associated with slight pitting edema at the ankles, but considerable wasting was also present.

In all those with mitral stenosis the normal ratio between total exchangeable sodium and potassium was lost. In healthy females the ratio of exchangeable sodium to exchangeable potassium is 1.02 while in healthy males it is 0.90. The corresponding ratios in the female and male patients with mitral stenosis were, respectively, 1.25 and 1.33, indicating a relative excess of sodium over potassium in their body composition.

In the comparisons shown in table 2 the only figures available for healthy adult females refer for the most part to a group with a mean age younger than that of the mitral stenosis patients. However, in the case of total body water there is probably a slight decrease with advancing years,[6] which renders the differences more striking. Little is known about the alterations in total exchangeable sodium and potassium with increasing age, but the available evidence does not suggest that there is any definite change between the third and fifth decades. For ease of reference the normal body composition of a healthy adult of similar weight to the patient with mitral stenosis has been calculated and is shown on the chart for comparison with the preoperative and later results (figs. 1*C*, 2*C*, 5 to 8, 11 and 12). The values shown in table 2 have been used for this purpose in females. The corresponding values for healthy young adult males are: total body water 62.0 per cent of body weight, exchangeable sodium 41.4 mEq. per kilogram, exchangeable potassium 46.8 mEq. per kilogram.[7]

POSTOPERATIVE CHANGES

Changes in Body Weight and Total Body Water. In the first six cases in which total body water was measured (cases 1 to 6 in table 1) the fluid intake in the immediate postoperative period was unrestricted. In these circumstances there was regularly an increase in weight after operation in spite of the negative nitrogen balance. Normally patients lose weight after surgery as a result of a number of factors.[1, 21] It is an outstanding abnormality of surgical metabolism for body weight to increase after operation. This was clearly due to water retention as was confirmed by the observations with deuterium oxide (figs. 1*C*, 5, 6, 9, and table 1). In cases 1, 3, 4, 5, and 6 measurements made within six days of operation all showed an increase in the total body water over the preoperative value. In

TABLE 2.—*Body Composition of Female Mitral Stenosis Patients before and after Operation in Comparison with Healthy Adult Females*

	Body Water					Exchangeable Sodium					Exchangeable Potassium				
	No.	Age	% Body Weight ± s.d.	t	p	No.	Age	mEq./Kg. ± s.d.	t	p	No.	Age	mEq./Kg. ± s.d.	t	p
Healthy females*	24	29.7	50.5 ± 4.7	—	—	12	27.6	39.6 ± 3.2	—	—	14	23.6	39.0 ± 5.4	—	—
Mitral stenosis before operation	9	43.2	54.5 ± 5.1	2.13	<.05 >.02	9	43.2	44.3 ± 5.1	2.70	<.02 >.01	8	41.9	35.4 ± 1.3	1.84	<.10 >.05
Mitral stenosis 3–6 mos. after operation	7	41.0	52.0 ± 5.4	.72	<.5 >.4	7	41.0	41.4 ± 4.2	1.05	<.4 >.3	7	41.0	36.8 ± 4.8	.91	<.4 >.3

* The figures for total body water and for exchangeable potassium in healthy females are taken from previously published results obtained in this laboratory.[6, 7] The figures for exchangeable sodium are a combination of the results in seven females reported by Forbes and Perley[3] and in five females studied in this laboratory; there was close agreement between these two series.

case 2 the measurement was made eight days after operation following a large water diuresis and an increase was not seen (fig. 2*C*). It is thus clear that in patients allowed unrestricted access to fluids, water retention readily occurred after operation even though the sodium intake was severely restricted. For example in case 3 there was a gain in total body water of 2.3 liters as measured on the fifth postoperative day, but the isotope studies showed an increase in exchangeable sodium of only 22 mEq. and by cumulative balance an increase of 55 mEq. Similarly, in all the other cases studied water was retained in considerable excess of sodium. The water retention persisted in these cases for the first week after operation but thereafter subsided. The measurements had all fallen to about the preoperative value by the time of discharge from the hospital which was usually between two and three weeks after operation.

In cases 7 through 11 the fluid intake was restricted to 1500 ml. a day for the day of operation and the early postoperative days. This figure does not include restoration of the operative blood loss and chest drainage fluid which were approximately covered by blood transfusions. In these cases with a strictly regulated fluid intake there was a steady loss of weight after operation and the total body water measurements no longer showed any definite increase but remained either approximately unchanged or slightly decreased (table 1 and fig. 7).

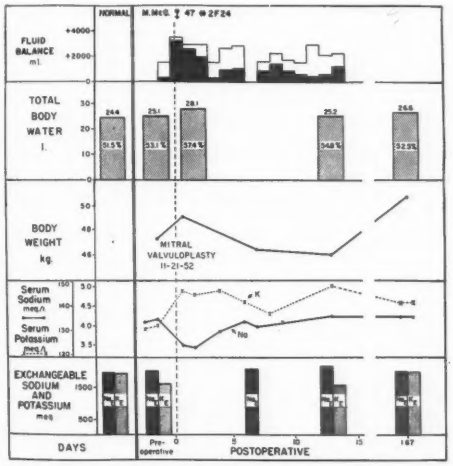

FIG. 6. Case 5. Charted as in figure 1*C*. The postoperative water loading, later excreted, with associated weight change is shown. The inverse sodium-potassium relationship in the serum is characteristic. The initial body composition shows an elevation in body sodium and a lowering of body potassium. In late convalescence (167 days after operation) body weight has increased significantly with a fall in total exchangeable sodium, and a rise in total exchangeable potassium. Although the absolute body water content has increased, the relative fraction (52.5 per cent of body weight) is at its lowest observed value, suggesting that body fat has been deposited.

Water Excretion in Relation to Total Body Water. The changes in total body water occur-

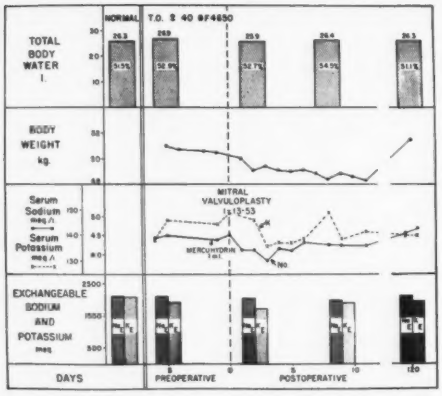

FIG. 7. Case 7. Charted as in figure 1*C*. Fluid intake was restricted to 1500 ml. There is no weight gain in the early postoperative period. Serum electrolyte changes are similar to those observed in other cases, but much less marked. Starting body composition shows a normal body sodium, and a lowered body potassium. Study in late convalescence (120 days) shows a return of body potassium towards normal. The total body water has now returned to normal in both absolute and relative terms.

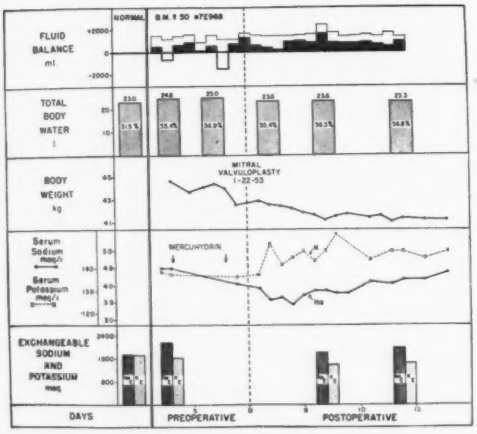

FIG. 8. Case 9. Charted as in figure 1*C*. See text for details.

ring shortly after operation can be correlated with water retention as shown by plotting the fluid intake and the urine output as a "balance." This clearly takes no account of extrarenal fluid loss, but nevertheless it shows that in those cases with considerable increases in total body water after operation there was a great excess of fluid intake over urine output

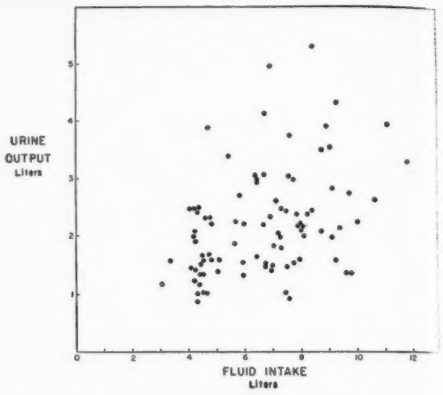

FIG. 9. Relationship between fluid intake exclusive of blood (abscissa, in liters) and urine output (ordinate, in liters). Each dot represents the total for the day of operation plus the two succeeding days, for a single patient. Data are based on study of 90 patients in all three of the fluid regimes discussed in the text. It will be noted that as fluid intake for these three days is increased over 4500 ml. a larger urine output (over 3000 cc.) results in only 12 instances. In all others the excessive fluid intake resulted only in excessive fluid retention. It should be noted that oliguria has been very rare in our experience with mitral stenosis surgery and therefore is but a very rare cause of the commonly observed hyperkaliemia.

(figs. 5 and 6). This was most noticeable during the day of operation and the first postoperative day when the urine output was always low even though the intake was extremely large. On the other hand the patients with a restricted fluid intake still maintained in this immediate postoperative period a urine volume similar to that seen in the unrestricted patients. In consequence there was no gross excess of fluid intake over output and no rise in total body water (figs. 7, 8, 9).

The ability of the kidney to excrete water during the first few days after a mitral valvuloplasty was studied more extensively by comparing three groups (30 cases each) in whom varying policies were followed with regard to fluid administration (table 3). All were investigated during the winter months when large cutaneous losses of water due to hot weather may be excluded. In one group of cases studied during this period (January to March, 1953), the mean total fluid intake exclusive of blood

TABLE 3.—*Changes in Urine Output and in Blood Chemistry Compared with Different Fluid Intakes. The Fluid Intakes and Urine Outputs Represent the Totals for the Day of Operation and the Two Succeeding Days*

Period of Study		No. of cases			Age Yrs.	Fluid intake for 3 days *ml.*	Urine output 3 days *ml.*	Blood transfusion. *ml.*	Blood and Serum Chemistry							
									Before Operation				On 2nd day after Operation			
		F	M	Total					Na *mEq./L.*	K *mEq./L.*	Cl. *mEq./L.*	BUN *mg./100 ml.*	Na *mEq./L.*	K. *mEq./L.*	Cl *mEq./L.*	B.U.N. *mg./100 ml.*
Gr. 1. 1/53	Mean	24	6	30	40.0	4400	1750	841	137.7	4.64	107.5	11.9	131.4	5.15	100.3	32.3
to 3/53	s.d.				5.7	410	630	634	4.6	0.38	4.1	4.4	4.9	0.59	4.6	21.0
Gr. 2. 10/52	Mean	25	5	30	41.5	7610	2340	1172	137.4	4.54	106.4	11.9	127.8	5.21	97.2	31.4
to 1/53	s.d.				8.4	1240	930	668	2.6	0.33	2.1	4.3	1.4	0.66	3.8	18.7
Gr. 3. 1/52	Mean	20	10	30	36.7	7860	2560	575	138.4	4.65	105.8	11.3	128.0	5.06	94.7	17.3
to 3/52	s.d.				6.7	1594	908	173	3.8	0.56	3.1	4.8	7.0	0.66	5.0	10.7

transfusion for the day of operation and the two succeeding days was 4400 ml., and the urine output 1750 ml. In the other two groups the patients were allowed to drink freely; intravenous infusions of 5 per cent dextrose solution were frequently given and the fluid intakes were consequently much larger. In the period October 1952 to January 1953, the mean intake of 30 cases was 7610 ml. over the same three days while the urine output was 2340 ml. Thus an increase of 3210 ml. in intake was only associated with a gain of 850 ml. in urine volume. Similar results were obtained in a group of 30 cases with unrestricted fluid intake studied a year earlier in the months January to March, 1952. In comparison with the restricted cases in the first group the intake in this third group was greater by 3460 ml. but the urine output only by 810 ml. The individual figures in these 90 cases are shown in figure 9, where it is apparent that in the majority of cases the kidneys were not able to respond proportionately to a large water load in the immediate postoperative period.

Sodium Metabolism. This was investigated by balance studies, by frequent measurements of serum sodium concentrations and by determinations of total exchangeable sodium at approximately weekly intervals. The sodium intake in all the cases was restricted, though to a variable degree. In cases 1 and 2, studied by both balance and isotope dilution technics, the sodium intake was approximately 40 mEq. a day (figs. 1*A*, and 2*A*). In case 3, also studied by both methods, the intake was only 9 mEq. a day (fig. 3) and a similar restriction was applied to cases 4 to 11 in whom isotope studies only were carried out.

In case 1 the patient was steadily retaining sodium both before and after operation as is shown in the cumulative balance chart (fig. 1*B*). This sodium retention continued up to the time of discharge from the hospital. In case 2 there was similarly preoperative retention of sodium, interrupted transiently by an injection of Mercuhydrin (fig. 2*B*). After operation sodium retention continued at approximately the same rate, but on the fifth day after operation a spontaneous sodium diuresis began and 500 mEq. were excreted in five days. Towards the end of the sodium diuresis an injection of Mercuhydrin was given, but this was clearly only responsible for a small part of the sodium excretion. Subsequently up to the time of discharge from the hospital there was a further period of steady sodium retention. In both these cases the isotope measurements confirmed the increase of sodium in the body (table 1). The initial preoperative measurements of total exchangeable sodium were in the upper part of the normal range and the further sodium retention accordingly led to unduly high values. In spite of this evidence of a growing excess of sodium in the body, the serum sodium concentration fell significantly after operation (figs. 1*B*, 2*B*). In case 1 this fall was from 138 mEq. per liter to 125 mEq. per liter, and in case 2 from 140 mEq. per liter to 125

TABLE 4.—*Comparison of Decreases in Serum Sodium and Chloride Concentrations on Second Postoperative Day in Three Groups of Patients Receiving Different Fluid Intakes*
(See table 3 for details)

	Changes in Serum Sodium			Changes in Serum Chloride		
	Mean decrease in serum sodium ± s.d. *mEq./L.*	*t*	*p*	Mean decrease in serum chloride ± s.d. *mEq./L.*	*t*	*p*
Group 1. Restricted fluids	6.3 ± 4.4	—	—	7.2 ± 4.9	—	—
Group 2. Unrestricted fluids	9.6 ± 3.4	3.27	<.005 >.001	9.2 ± 4.9	1.59	<.2 >.1
Group 3. Unrestricted fluids	10.4 ± 6.3	2.93	<.005 >.001	11.1 ± 6.6	2.60	<.02 >.01

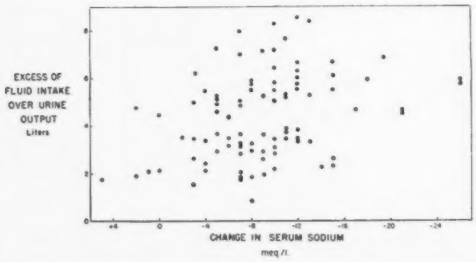

FIG. 10. Relationship between serum sodium change (abscissa, in mEq. per liter) and excess of fluid intake over output (ordinate, in liters) based on the same three-day periods, indicated in figure 13. Data are based on the same 90 patients shown in figure 13. It will be noted that as fluid intake exceeds output by greater volumes, there is a tendency to lower the serum sodium more markedly. However in the lower intake ranges (excess over output being 2.5 liters or less) considerable drops may still be seen and correlation is less clear cut.

mEq. per liter. The levels were restored slowly after operation. In case 2 it is of considerable interest that the rise in serum sodium concentration began immediately before and continued during the large sodium diuresis (fig. 2*B*).

In the other cases with the more severely restricted sodium intake there was no opportunity for any significant degree of sodium retention. In case 3 the cumulative balance (fig. 4) and the isotope dilution studies (table 1) showed no sodium depletion. Nevertheless, after operation the serum sodium concentration fell sharply from 141 mEq. per liter to 122 mEq. per liter (fig. 5). Thereafter it rose slowly and was finally restored to the preoperative level. The large changes in serum sodium concentration observed in this case clearly occurred without any significant changes in the amount of sodium in the body. Similar observations were made in cases 4, 5 and 6 in whom definite postoperative decreases in serum sodium developed with, at the same time, slight increases in the total exchangeable sodium (table 1 and fig. 6).

In cases 1 to 6 fluid was given freely, but even when the fluid intake was restricted so that there was a progressive fall in body weight and no increase in total body water after operation the serum sodium concentration still fell (fig. 7). Further evidence was sought by comparing measurements made preoperatively and on the second postoperative day in the three groups of cases, 90 in all, described above (table 3). In the two groups with unrestricted fluid intakes the decreases in serum sodium were greater than in the group with restricted fluid intake. Specifically, the unrestricted groups showed mean postoperative serum sodiums of 127 and 128 mEq. per liter while the restricted group was 131 mEq. per liter. These are averages of three groups of 30 cases each. Statistical analysis shows that these differences are significant (table 4), and in both instances the comparisons contrast unrestricted fluid regimens with the restricted group. There is thus some relation between the excess of fluid intake over urine output and the extent of the decrease in serum sodium concentration. The larger falls in serum sodium were usually seen in those patients showing considerable fluid retention (fig. 10). It is, how-

ever, quite clear that decreases in serum sodium concentration still occurred even in the presence of a low fluid intake and adequate urine volume.

Persistent Low Serum Sodium Concentrations. It is to be emphasized that in the majority of cases the transient fall in serum sodium characteristically observed after operation was not associated with any loss of sodium from the body and occurred in patients having adequate amounts of total exchangeable sodium. Usually the serum sodium began to rise on the fourth or fifth postoperative day and thereafter steadily climbed to the normal range. However, in a certain number of cases the serum sodium level either before or after operation was persistently low. This condition was particularly seen in severely disabled patients kept strictly on a low sodium diet and treated vigorously with mercurial diuretics. In them the measurements of total exchangeable sodium often showed some evidence of salt depletion. The following case is illustrative of those few which showed sodium depletion prior to operation.

Case 8 was that of a female with severe mitral stenosis and auricular fibrillation who had been treated with a low salt diet for six months prior to operation. On admission to the hospital there was no peripheral edema but there was hepatomegaly and considerable pulmonary congestion. She was accordingly given several injections of Mercuhydrin before operation (fig. 11). On the day before operation the serum sodium was only 133 mEq. per liter and the total exchangeable sodium was 1575 mEq. or 33.5 mEq. per kilogram, a low figure for a person of her slim build. After operation the fluid intake was restricted to 1500 ml. a day; there was a slow loss of weight and a slight gain in total body water. The serum sodium fell to 125 mEq. per liter in which region it remained for nine days in spite of a highly successful valvuloplasty. A total exchangeable sodium measurement on the seventh postoperative day showed an increase of 78 mEq., confirming that the losses of sodium from hemorrhage at operation and in chest drainage fluid had been adequately restored. During this period she was clearly not making good progress. She could only think and speak slowly though there was no evidence of any definite paralysis. She was largely indifferent to her surroundings and was frequently incontinent of urine.

On the tenth postoperative day she was given an infusion of 3 per cent sodium chloride yielding 240 mEq. of sodium. During the 24 hours from the beginning of this infusion the total fluid intake was 1250 ml., and the urine output of 650 ml. contained a total of 7 mEq. of sodium. Thus 237 mEq. of sodium was retained in the body after 24 hours; at the same time the serum sodium had risen from 125 mEq. per liter to 131 mEq. per liter. Thereafter there was a great improvement in her general condition and a slow steady rise in the serum sodium concentration to 142 mEq. per liter even though the sodium intake was kept at 9 mEq. a day. The total exchangeable sodium, measured five days after the infusion, when the serum sodium had reached 138 mEq. per liter, was 1855 mEq., an increase of 202 mEq. over the reading before the infusion. At the same time the total body water had increased by 0.9 liters. Further measurements were made 118 days after operation, when she was

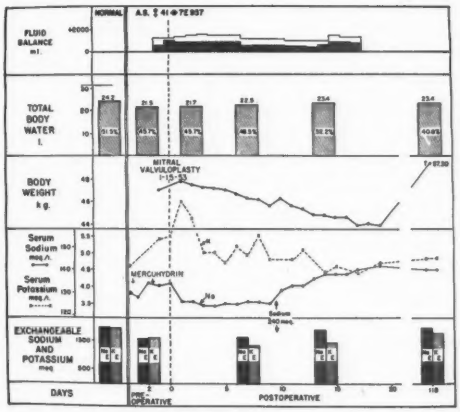

FIG. 11. Case 8. Charted as in figure 1*C*. Fluid intake was restricted and is remarkably constant. There is weight gain for one day only, followed by a steady loss until discharge. Serum electrolytes show several significant points. Sodium, low to begin with, falls after operation and is persistently low. On the ninth postoperative day a sodium load of 240 mEq. was given as 3.0 per cent sodium chloride. The effect on serum sodium is initially very small, but is followed by a rise which persists to normal values. The potassium rises rapidly to high levels (6.5 mEq. per liter), falls abruptly without specific therapy, and later falls further as the sodium rises. Body composition is initially remarkable in that there is a low total exchangeable sodium as well as the expected low total exchangeable potassium. Study in late convalescence shows a return of all values toward normal along with a gain of 10 Kg., one of the largest observed. It is of great significance that with this weight gain the water fraction of body composition falls to 40.8 per cent, indicating a large accumulation of fat.

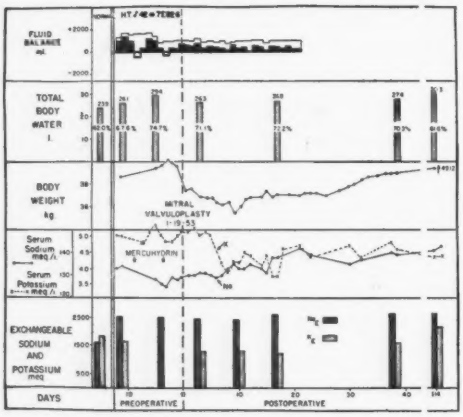

FIG. 12. Case 11. Charted as in figure 1*C*. Clinical details are described in the text. Serum electrolytes show change similar to case 8, figure 11; sodium is low preoperatively and goes lower as weight and water are gained; postoperative changes are not marked. The potassium is initially high but postoperatively does not rise further. Starting body composition is remarkable for its large excess of sodium, and the remarkably low body potassium as postoperative changes become apparent. The total body water at 74.7 per cent of body weight is among the highest observed, and was borne out by the remarkable cachexia seen clinically. In late convalescence (114 days) weight gain has been marked (11 Kg.); the water fraction has fallen to 61.6 per cent of body weight. Although the progression of body composition toward normal has been great, the patient at this time still has a relatively high total body water, and his body sodium-potassium ratio is still elevated.

in excellent health, had gained 12.5 Kg. in weight and had an enormously improved exercise tolerance. The results at this time are shown in table 1, and, using these figures for comparison, there is evidence that there was a deficiency of sodium in the body when she came to operation. At that time she had 1575 mEq. of exchangeable sodium in contrast to 1915 mEq. when she was in good health. Normal serum sodium concentrations were only attained when this deficiency was restored.

Similar features were seen in case 9, a female with a tight mitral stenosis, minimal aortic regurgitation and auricular fibrillation. On admission the serum sodium concentration was 140 mEq. per liter and the total exchangeable sodium 2219 mEq. or 49.6 mEq. per kilogram. She was treated preoperatively on a 9 mEq. a day sodium diet, mercurial diuretics and ammonium chloride. On this regime the total body water did not change but the serum sodium concentration fell to 133 mEq. per liter before operation (fig. 8). The estimated loss of sodium through hemorrhage and chest drainage was about 150 mEq. but she only received about 90 mEq. in the transfusions given at operation. The postoperative measurement of total exchangeable sodium was only 1871 mEq., a decrease of 348 mEq. The serum sodium concentration fell to 125 mEq. and was unduly slow in returning to the normal range, reaching only 135 mEq. per liter on the fourteenth postoperative day; at this time the sodium deficiency was still 264 mEq. in comparison with the preoperative reading. In this case the large sodium loss resulting from the mercurial diuretics and operation apparently impeded the restoration of the serum sodium concentration.

In the two cases described above fluid intake was restricted to 1500 ml. a day, and there was no evidence of water retention when the serum sodium concentration was persistently low. Retention of water without sodium may, however, occur preoperatively as is illustrated in the following case.

Case 11 was that of a male who had been severely disabled with mitral stenosis and auricular fibrillation for several years. During the last two years his condition deteriorated rapidly and for some time before study he was confined to bed with extreme respiratory distress even at rest. He had lost a large amount of weight. On admission, he was grossly emaciated, there was some peripheral edema and the serum sodium was 138 mEq. per liter. After treatment with mercurial diuretics and restriction of sodium intake to 9 mEq. per day the peripheral edema disappeared but the serum sodium fell. When the detailed preoperative studies were begun (fig. 12) the serum sodium was 134 mEq. per liter, the total exchangeable sodium 2507 mEq., or 64.9 mEq. per kilogram and the total body water 26.1 liters. His condition began to deteriorate further and he became more breathless, apathetic and disorientated. He slowly gained weight. A week later the serum sodium was 126 mEq. per liter, the total body water 29.4 liters and the total exchangeable sodium 2501 mEq. Thus he had gained 3.3 liters of water without any increase in body sodium. After this measurement his fluid intake was restricted to 1 liter a day, he lost weight and the serum sodium concentration rose slightly. There was some improvement in his general condition and a successful valvuloplasty was carried out under local anesthesia despite the apparently preterminal state of the patient. The fluid restriction was continued, there was no further fall in serum sodium concentration and there was a conspicuous improvement in his condition. The total body water on the third postoperative day was 26.3 liters. Subsequently the serum sodium concentration rose

steadily to normal, and there were small increases in total body water and exchangeable sodium. On the thirtieth postoperative day he was changed to a high calorie diet with a sodium intake of 35 mEq. a day. Thereafter, while in the hospital, he gained weight steadily with only slight further increases in total body water and exchangeable sodium but a considerable rise in total exchangeable potassium. In this case the results suggest that there was a small deficiency of sodium in the body before operation when the serum sodium was low despite the apparently high figure for exchangeable sodium on a body weight basis. The striking feature, however, was the ease with which he retained water at this time, leading to a further depression of the serum sodium.

Potassium Metabolism. This was investigated by the same methods as in the sodium studies. In all cases there was a loss of potassium from the body after operation clearly shown in the balance studies and confirmed by the isotope dilution measurements (figs. 1*A*, 2*A*, 7 and table 1). Coincident with this large excretion the serum potassium concentration rose. This was a constant finding in all the cases studied (figs. 1*C*, 2*C*, 5–8). The increased potassium excretion was at its greatest on the day of operation despite the oliguria and did not persist for so long as the increased nitrogen excretion. The extent of the rise in serum potassium concentration could not be correlated with the amount of blood transfused at operation, the fluid intake in the immediate postoperative period or the volume of urine excreted (table 3). There appeared to be a definite inverse relationship to the serum sodium concentration, as the largest falls in the latter were invariably accompanied by considerable increases in the serum potassium concentration. Furthermore in those cases where the serum sodium concentration was persistently low either before or after operation the serum potassium remained consistently high (figs. 8, 11, 12) and only fell when the serum sodium concentration rose.

Correlation of Isotope and Balance Measurements of Sodium and Potassium. In cases 1 to 3 the results of the isotope dilution studies may be checked against the cumulative metabolic balances for sodium and potassium. This comparison is summarized in table 5 where the changes from the preoperative to the last measurement before discharge from the hospital are shown. During this period of three to four weeks there is good agreement between the sodium measurements. In two of the potassium studies the correlation is also reasonably close, but in case 3 there is some discrepancy between the two methods, the isotope measurements showing a greater loss of potassium than can be accounted for in the balance study. The extent of agreement that may be anticipated between the two methods has been more fully reviewed elsewhere.[13, 14, 15]

Chloride Metabolism. This has been studied only by measurement of serum concentration before and after operation. In general the changes ran parallel to those found in sodium concentrations. After operation there was a considerable fall (table 3), and this was affected in the same way as the sodium by restricting the fluid intake (table 4). The scatter in the chloride determinations was, however, greater and the changes do not attain such a high degree of significance.

Changes in Blood Urea Nitrogen. These were studied in the three groups of cases shown in Table 3. There was invariably a rise in blood urea nitrogen after operation related to at least two factors, namely the size of the blood transfusions given at operation and the fluid intake and urine output after operation. The rise was least in group 3 where the smallest blood transfusions were given and fluid intake was unrestricted; in both groups 1 and 2 the rises were larger and approximately similar, but in the group 2 cases the blood transfusions and fluid intake were greater than in the group 1 cases.

TABLE 5.—*Comparison of Changes in Sodium and Potassium in the Body as Measured by Metabolic Balance and Isotope Dilution*

	Interval, days	Change in Sodium		Change in Potassium	
		Balance *mEq.*	Isotope *mEq.*	Balance *mEq.*	Isotope *mEq.*
Case 1.....	21	+250	+208	+55	−90
Case 2.....	28	+250	+198	−75	−141
Case 3.....	22	+76	+189	−44	−337

Changes in Late Convalescence

Nine patients returned for further studies between three and six months after discharge from the hospital. In all a good functional result had been obtained. Their exercise tolerances were greatly improved. In the majority (cases 1, 2, 4, 5, 7, 8, and 11) there was a corresponding improvement in nutritional state following the operation. The striking features were the gain in weight and the return of the body composition toward normal (table 1 and figs. 1*C*, 2*C*, 5–7, 11, 12). In case 6, however, convalescence had been complicated by the development of two attacks of pneumonia and pleurisy. She had lost weight and her general condition had deteriorated in spite of considerable relief of her dyspnea. Her body composition was still abnormal. In case 3, although the cardiac symptoms had greatly improved so that she was able to lead a practically normal life, there was persistent anorexia after operation, possibly due to high digitalis dosage, and she had failed to gain weight.

The results in seven female patients, three to six months after operation, are shown compared with the healthy adults and the preoperative measurements in table 2. Case 6 has been excluded from this group as she was not fully recovered from the pneumonia when the measurements were made. These patients now show no significant differences as regards body composition in comparison with the healthy adults. In case 1 a further study was possible one year after operation; she continued to gain weight and lose sodium over this period. In the male patient, case 11, who had been greatly emaciated, some restoration of body composition towards normal had occurred after 114 days (fig. 12). Even though he had gained over 10 Kg. in weight the process was still clearly incomplete. With improved cardiac function he was rebuilding muscle mass rapidly and in 114 days had increased his total exchangeable potassium from 1290 mEq. to 2097 mEq., almost double the earlier figure. His water fraction had lowered from its high value of 74.7 per cent to 61.6 per cent, as clear evidence of fat accumulation. At this time his clinical appearance was that of a most dramatic "filling out" of subcutaneous fat, and muscular masses; no longer bedridden, he was active about the house.

His total exchangeable sodium was still elevated as evidence of some further metabolic convalescence yet to be completed.

Discussion

Disordered Biochemistry. The body composition of the patients with mitral stenosis before surgery showed certain abnormal features when contrasted with that of healthy adult women, namely a relative excess of sodium and water. Such features are, of course, commonly seen in edematous patients,[16, 17, 18] but in these cases no clinically detectable edema was present at the time of the measurements. These changes may also be seen as a result of undernutrition[17, 19] and of various chronic wasting diseases[20] which lead to a loss of cell mass and of fat. Chronic cardiac disease undoubtedly falls into this category and the preoperative body composition is probably due to the wasting rather than latent edema. In this respect it is of interest that with the gain in weight seen over the course of several months after a successful valvuloplasty the proportions of water and sodium in the body decrease, as the exchangeable potassium rises. This is clear evidence of an increasing muscle mass, and an increasing store of body fat. Taken together, these indicate a reversal of the "syndrome of depletion" and a rebuilding of those energy-exchanging and energy-storing tissues vital to an active existence.[8] Taken together these changes are a most eloquent witness to the effectiveness of the valvuloplasty itself; where cardiac function is slow to return, or fails to return, such restorative changes are not seen. Similar changes are seen in the rehabilation of those suffering from chronic undernutrition[19] and in convalescence from a successful surgical operation.[20, 21]

Immediately after operation several complex changes develop, which are common to all types of trauma and are in no way peculiar to those undergoing mitral valvuloplasty. These features, which are also regularly seen in patients without cardiac disease, include the increased nitrogen excretion,[1, 21] the loss of potassium in excess of nitrogen,[1] the fall in eosinophil

count[22] and the rise in urinary excretion of 17-ketosteroids and 17-hydroxycorticoids.[23] In noncardiac patients also, postoperative retention of water, decrease in serum sodium and elevation of serum potassium concentration frequently occur.[1, 24, 25] However, in patients with mitral stenosis undergoing surgery these changes are often extremely conspicuous and merit further consideration.

The mechanism of the changes in serum sodium concentration seen postoperatively is obscure. The results reported here clearly show that the serum sodium concentration falls postoperatively even though there is no loss of sodium from the body and, more strikingly, even where sodium loading is occurring. Retention of water may play a part, but when the fluid intake is restricted so that no apparent increase in total body water occurs a definite decrease in sodium concentration still develops. Figure 10 offers graphic evidence that in general there is a poor correlation between water retention and postoperative hyponatremia. Thus the evidence suggests that "external dilution" is not the only significant factor, if it is assumed that the retained water is evenly distributed over the body. Clearly, if fluid were held preferentially in the extracellular fluid, only a small amount would be required to produce a definite decrease in the sodium concentration. Changes in total body water of under 1 liter cannot be detected with confidence by the deuterium oxide method.

Other factors that may be of importance are movements of electrolytes and water between the intracellular and extracellular compartments. After operation potassium leaves the cells in considerable quantity and is rapidly excreted at a time when there is marked oliguria. It is possible that at the same time water moves out of the cells into the extracellular fluid where it is retained and dilutes the sodium and chloride ("internal dilution"). Thirst is a prominent postoperative symptom and may possibly be associated with such a cellular dehydration.[26] Alternatively sodium may move into the cells replacing potassium, though direct measurements have not yet shown such a transfer in patients with medically treated heartfailure,[27] or may enter bones or the gastrointestinal tract which both contain large stores of sodium.[28, 29, 30]

In patients with a persistently low serum sodium concentration, either before or after operation, several factors may be at work. Sodium depletion may develop as a result of a low sodium diet and treatment with mercurial diuretics[31, 32] or from inadequate restoration of sodium lost in hemorrhage at operation and through drainage of fluid from the chest. Excessive retention of water readily occurs in sick patients placed on a low sodium diet, particularly if they are subjected to the stress of an operation or respiratory infection. Certain of the features seen in the mitral stenosis patients after operation may be reproduced by the administration of antidiuretic hormone. This leads to retention of water, depression of serum sodium concentration and the development of symptoms associated with water intoxication.[33,34] In patients with heart disease and a low serum sodium concentration there is persistent antidiuretic activity.[35]

Therapeutic Considerations. From the practical therapeutic point of view certain general principles emerge from this study. Patients undergoing mitral valvuloplasty show all the postoperative features commonly seen in general surgical cases. Their significance and therapeutic implications have been described elsewhere.[1] However, the disturbances of fluid and electrolyte metabolism tend to be unduly large in comparison with noncardiac patients and it is in dealing with them that additional care is often required.

In one of the groups, the majority, the serum sodium concentration is normal before operation and the total exchangeable sodium is high. The postoperative fall in serum sodium is not due to body sodium depletion and constitutes part of the physiologic response to trauma. It is transient, is not harmful to the patient and is not an indication for the administration of extra sodium. After operation the patient will readily retain water even in the absence of salt. Excessive fluid intake at this stage depresses still further the serum sodium concentration and may aggravate the patient's condition. Thirst is not a reliable indication of dehydration; it may be present even though there has

been fluid retention of over 3 liters. The most valuable indications in regulating the fluid intake are the patient's weight and urine volume. A series of preoperative weight measurements is of great assistance as a loss normally occurs after operation due to metabolism of fat and lean tissue.[1] If the weight remains steady or increases, excess water is clearly being retained. In general, in a patient of average size the fluid intake in the days immediately after operation should not exceed 2000 ml. a day unless there are special indications such as for example high fever, unduly hot weather, or large drainage from the chest. Similarly the daily excess of fluid intake over urine volume should not be greater than about 1500 ml. unless an exceptionally large extrarenal loss of fluid can be demonstrated.

In another group of patients, a minority, the serum sodium concentration is persistently low. Before operation in the nonedematous patient this is suggestive of salt depletion due to a combination of low sodium diet and administration of mercurial diuretics.[31] The condition may be aggravated or appear later if the sodium loss at operation is not fully replenished. In the postoperative period sodium depletion may be suspected if the serum sodium has not begun to rise after a week from the date of the valvuloplasty and the case is otherwise uncomplicated. In these circumstances administration of hypertonic saline and fluid restriction are indicated to return the body composition to normal. It is very important to emphasize that a persistent low plasma sodium either before or after operation may occur in the absence of sodium depletion (an example is found in case 11, figure 12) and with the "high body water, high body sodium, low body potassium" syndrome of depletion. In such patients water restriction and caloric intake are of much greater importance than giving sodium. High dosage of the latter even over short periods may lead to disastrous pulmonary edema *while the plasma sodium still remains low.* In this second group with a persistent low plasma sodium, therefore, one must approach sodium therapy with great caution and search diligently for evidence of true sodium depletion before giving over 150 mEq. of sodium. The urine sodium concentration should be determined in all such cases to avoid overlooking the rare "urinary salt loser" in whom energetic sodium replacement is vital.

In none of these patients was the elevation of serum potassium associated with indisputable evidence of potassium toxicity. Were such to occur in the postoperative period, the administration of hypertonic saline intravenously might be of benefit. Such a benefit has been observed in other cardiac surgical patients and in surgery undertaken during the uremic state.

When edema is present, even in minimal amounts, restriction of fluid intake to 1200 to 1500 ml. a day often alleviates hyponatremia, and sodium administration with its hazard of increasing already expanded stores of salt and water may be avoided. However, if hyponatremia exists with symptoms such as disorientation, delirium, muscular weakness, apathy or stupor, hypertonic saline and fluid restriction are indicated for the rapid relief of these manifestations.

A quick restoration of the serum sodium level should not be anticipated or attempted. Measurements of total body sodium have shown that after an adequate amount of sodium has been given there may be only a relatively small immediate rise in serum sodium as readjustment of the balance between sodium and water in the body apparently requires several days. In brief:

1. *Where surgery has been successful and caloric intake can be resumed* the electrolyte pattern will be observed to restore itself gradually to normal if water and salt loading are avoided. The reciprocal nature of the changes in body sodium and potassium and in plasma sodium and potassium will be noted. This restoration is merely a biochemical index of general convalescent rehabilitation.

2. *Where surgery has not been successful and caloric intake remains restricted* the electrolyte pattern remains distorted, the syndrome of depletion is unrelieved and, in our experience, a wide variety of maneuvers designed for "passive" restoration of water and electrolyte to normal are quite unavailing.

3. Finally there is a third or intermediate group where *preoperative depletion has been*

maximal, surgical convalescence is slow and caloric resumption hesitant. In these cases, water and salt restriction, daily weight measurement and caloric forcing are indeed life-saving measures. In addition, as mentioned above, hypertonic saline may be given intravenously under the following circumstances, using 250 cc. of 3.0 per cent sodium chloride: (a) Where plasma potassium is dangerously high and electrocardiographic evidences of toxicity are manifest. (b) Where there is a persistent low sodium without edema, fluid is being restricted, caloric intake has begun, and weight is constant or falling. Here a small dose of hypertonic saline will occasionally initiate a gradual restoration of the plasma electrolyte pattern to normal. This indication is clear if true sodium deficiency can be established by history or Na_E, as in case 8, fig. 11. (c) Where an acute depression of plasma sodium after operation progresses to 120 mEq. per liter or below, with associated symptoms. Here again a single dose of hypertonic saline given with caution may be of emergency value even though it appears to exaggerate the high body sodium aspect of the patient's disorder.

Summary

The effect of severe mitral stenosis on body composition has been studied before and after valvuloplasty.

In nonedematous patients immediately before operation there was a slight excess of sodium and water, and a depression of body potassium.

Immediately after operation the general features of a response to severe trauma were seen, such as an increased nitrogen and potassium excretion, retention of sodium, a fall in eosinophil count and an increased urinary steroid excretion. The changes in water and electrolyte metabolism were of the same nature but frequently greater in degree than those commonly seen in noncardiac patients after operation. Water retention readily occurred in spite of severe restriction of sodium intake. The serum sodium and chloride concentrations fell and the potassium rose. The fall in serum sodium was not due to loss of sodium from the body; it was greater in those showing considerable water retention but this was not the sole cause. In a few cases a combination of low salt diet, mercurial diuretics and incompletely restored operative loss led to salt depletion and a persistently low serum sodium concentration.

Body composition slowly returned towards normal over a period of many months after a successful operation. The gain in weight was due to the restoration of lean tissue and fat.

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Sumario Español

Pacientes con decompensación cardíaca crónica operados para la correción quirúrgica de la estenosis mitral han sido repetidamente observados tener una concentración baja de sodio plasmático y una concentración alta de potasio plasmático luego de la operación. Este estudio fué principalmente encaminado a investigar estas anormalidades. Los autores han demostrado quel el paciente preoperatorio tiene un desorden característico de composición orgánica, notable por una cantidad grande total de agua, una cantidad alta total de sodio, una cantidad total baja de potasio intercambiable y una concentración de sodio plasmático baja. Los efectos de la cirugía en esta composición anormal del cuerpo y las implicaciones terapéuticas se discuten.

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Tumor Metastasis to the Heart

By J. M. Young, M.D., and I. Ralph Goldman, M.D., F.C.C.P.

This article is a survey of 476 consecutive cases of tumor death for heart involvement. The somewhat selected group of cases (from a Veterans Administration hospital) shows an incidence of cardiac metastasis of 19.1 per cent. The bulk of tumors metastasizing to the heart were bronchogenic carcinoma, malignant melanoma, malignant lymphoma, and carcinoma of the pancreas and esophagus. Electrocardiographic changes were frequent and correlated fairly closely with the anatomic extent of the disease. The related literature is reviewed.

MYOCARDIAL involvement by neoplasms arising elsewhere in the body is no longer considered rare. A survey of the literature discloses a gradually rising incidence of myocardial metastasis as this subject is more closely explored. It has recently been estimated that more than 500 instances of tumor metastasis to the heart are now recorded, and more than 20 of these were diagnosed before death.[1] In the earlier literature, summarized by Morris,[2] Yater,[3] Lisa and co-workers,[4] Doane and Pressman,[5] and Willis,[6] one finds that the incidence figures were almost always below 2 per cent. Often, however, the number of tumor deaths was not mentioned. Carcinoma of the breast, lung, esophagus, pancreas, malignant melanoma, and malignant lymphoma are mentioned most frequently in the literature as the primary tumor. In fact, almost all types of tumors have occasionally metastasized to the heart. Very often the total of tumors of each kind is not given. Notable exceptions are the series of Herbut and Maisell[7] and Willis.[6]

Scott and Garvin[8] found a 10.9 per cent incidence of cardiac involvement in 1082 cases of tumor death. Likewise, Dimmette[9] reported a figure of 8.35 per cent in 455 cases. This present report does not represent the expected frequency of cardiac metastasis in a general hospital, but rather that found in a large general medical and surgical Veterans Administration hospital which is also a reference center for thoracic surgery and for many cases of malignant lymphoma. Another factor in our high incidence is probable longer survival of our cases, since many remained hospital cases throughout their terminal course. This longer survival likely has allowed more widespread metastasis.

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Material

During approximately six and one-half years 1400 autopsies have been performed, and 586 of these were upon patients who had died of tumor (41.9 per cent). Leukemia cases and brain tumors have been excluded, since the former show cardiac infiltrations frequently, and the latter almost never metastasize outside the central nervous system. (See table 1.) In 54 cases of leukemia there were 25 with myocardial infiltrations, and seven of these were of moderate or marked degree (fig. 1). Fifteen of 30 granulocytic leukemia cases and 5 of 16 lymphoid leukemia cases disclosed cardiac infiltrations.

In the remaining 476 cases of tumor death there were 91 with cardiac involvement, an incidence of 19.1 per cent. Examination of table 2 explains this high percentage since a large proportion of our cases have been bronchogenic carcinoma, malignant melanoma, malignant lymphoma, and carcinoma of the pancreas and esophagus. Six of these cases have been reported previously in detail by Lefkovits.[10] In all cases there were metastases to sites other than the heart.

In most of the reported series the right side of the heart has been more frequently involved than the left, but in some series[6-8] more nearly equal involvement of the right and left sides has been noted. In our cases with hematogenous metastases, the right side was involved alone in but seven cases, the left side in 13 cases, and both sides in nine cases. There was bilateral involvement, considering all metastatic pathways, in 63 cases and endocardial involvement only in two cases. In the other six cases insufficient

Table 1.—*Incidence of Cardiac Metastases*

Total Autopsies	1400
Tumor Deaths	586 (41.9%)
Tumor Deaths Less Leukemias and Brain Tumors	476
Cases with Heart Metastases	91 (19.1%)

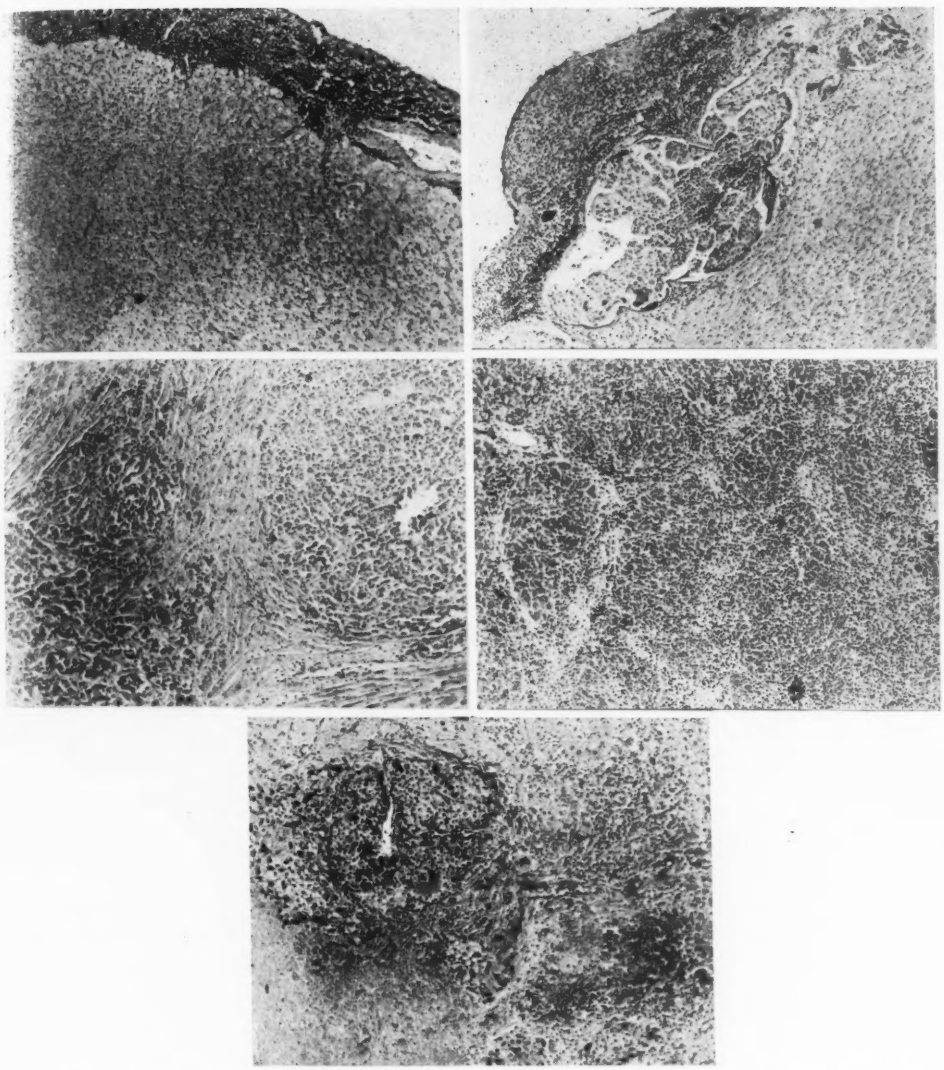

FIG. 1 (*top left*). Subepicardial and myocardial infiltration in chronic granulocytic leukemia. (× 45)

FIG. 2 (*top right*). Bronchogenic carcinoma. Note dilated lymphatics filled with tumor tissue and the accompanying inflammatory reaction. (× 45)

FIG. 3 (*middle left*). Myocardial tumor nodules in malignant melanoma. (× 45)

FIG. 4 (*middle right*). Lymphocytic lymphosarcoma. Note widespread invasion and separation of muscle fibers and bundles. (× 45)

FIG. 5 (*bottom*). Testicular tumor with hematogenous chorionepithelioma cardiac metastasis. Note necrosis accompanying tumor. (× 45)

d· a were given to classify the extent and locations o· he metastases.

The epicardial and subepicardial lymphatics were n st often involved in our cases. Sixty cases showed i· olvement in this manner, while 29 had myocardial (hematogenous) metastases and two had endocardial implants. In the group with subepicardial lymphatic involvement, the right side of the heart, particularly the auricle, was most affected. In most cases the extent of the metastasis was grossly

TABLE 2.—*Tumor Types with Percentages Showing Heart Metastases*

Primary Site	Total Cases	Metastasis to Heart	Percentage
Bronchus	109	40	36.7
Malignant Melanoma	17	11	64.7
Malignant Lymphoma	60	9	15.0
Pancreas	33	7	21.2
Esophagus	33	6	18.2
Kidney	15	4	26.7
Testicle	9	4	44.4
Stomach	34	2	5.9
Prostate	27	2	7.4
Bladder	15	1	
Larynx	11	1	
Skin	5	1	
Adrenal	3	1	
Paranasal Sinus	2	1	
Lip	2	1	

evident, but in 12 the metastases were of microscopic proportions. No case having only parietal pericardial involvement is included as a case with metastasis.

The high incidence of mediastinal involvement in tumors metastatic to the heart has been noted by many observers, and this has been stressed particularly by Morris[2] and Lymburner.[11] The filling of the lymph nodes and mediastinal tissues blocks the lymphatic channels draining the heart and allows retrograde extension through the subepicardial lymphatic vessels. In this series the mediastinum was significantly involved in 66 cases (72.5 per cent); this was very evident in the cases of bronchogenic carcinoma where 37 of the 40 cases had mediastinal involvement.

Electrocardiograms were available for study in 35 cases. We have excluded 12 because of prior changes due to other forms of heart disease. The remaining 23 were obtained within six months of the time of death, and a summary of the findings correlated with the anatomic changes is presented in table 3. There was positive correlation in 16 instances; the changes noted most frequently were sinus tachycardia (11 times), low voltage (10 times), changes typical of pericardial or myocardial involvement (10 times), auricular fibrillation (four times), auricular flutter (three times), varying degrees of A-V block (two times), and bundle branch block (one time). In 14 cases the electrocardiographic tracings were taken within one month of death. While the various rhythm changes and degrees of block were often transient, low voltage, once it appeared, remained. Low voltage often accompanied pericardial effusion and obliteration of the pericardial sac by tumor and adhesions.

TUMORS BY TYPES

Bronchogenic Carcinoma

In the 109 cases in this group, 40 disclosed cardiac involvement. Twenty-three tumors arose in the right lung, 16 in the left lung, and one was a terminal bronchiolar carcinoma with bilateral involvement. In 37 of the 40 cases there was definite mediastinal involvement, and this most often was marked. The route of involvement was via the lymphatics (retrograde extension) in 34 cases and hematogenous in six. In the cases showing subepicardial tumor, the right auricle was usually more markedly involved (see fig. 2).

The pericardial sac was obliterated by tumor and adhesions in seven cases. There was significant pericardial effusion in 14 cases; this was sanguineous in eight. The heart weight was above 350 Gm. in 16 cases, but only two of these weighed more than 550 Gm.

Electrocardiographic tracings were made in 16 cases. Table 3 lists the cases and correlates the anatomic findings and electrocardiographic changes. Those showing low voltage usually had obliteration of the pericardial sac or pericardial effusion. A pattern of epicardial or myocardial involvement was present in six tracings, and in two of these, serial tracings disclosed partial resolution of the process.

Malignant Melanoma

This tumor most often involves the heart by the hematogenous pathway (see fig. 3). Eleven of our 17 cases disclosed cardiac metastases (64.7 per cent), and in eight the metastases were blood-borne. In three there was significant serous pericardial effusion. Mediastinal involvement was notable in five cases, and three of these showed subepicardial metastases. Heart weight was increased in three cases where numerous tumor nodules were present. In one case, these nodules ulcerated through the endocardium, resulting in implants between the trabeculae and on the valves. Unfortunately, in only one case was an electrocardiogram taken. This disclosed low voltage and a pattern suggestive of myocardial spread.

TABLE 3.—*Correlation of Anatomic Findings and Electrocardiographic Changes*

Case	Anatomic Findings	Electrocardiographic Changes	Correlation
	Bronchogenic Carcinoma		
(1) P.M. 162	Obliteration of pericard. sac by fibrous adhesions and tumor.	Low voltage. Complete A-V dissoc. Inverted T in CF_5. Ventric. premature systoles. This later showed P pulmonale with a prolonged Q-T interval.	Pos.
(2) P.M. 350	Many tumor nodules through subepicard. region with infiltration of outer layer of myocard.	Inverted T wave in CF_2. Last tracing obtained 35 days before death.	Neg.
(3) P.M. 361	Subepicard. lymphatic and pericard. involvement by tumor tissue.	Normal ECG taken 24 days before death.	Neg.
(4) P.M. 374	Numerous tumor nodules in left aur., right vent. and I.V. septum, and one nodule present in septum between the tricuspid and mitral valve rings.	Pattern of left bundle branch block.	Pos.
(5) P.M. 482	Slight subepicard. lymphatic involvement with invasion of outer layer of myocard.	Digitalis effect. Last tracing taken 18 days before death.	Neg.
(6) P.M. 537	Sanguineous pericard. effusion. Marked subepicard. lymphatic involvement with infiltration of outer myocard. layer by tumor tissue.	Sinus tachycard. changing to auric. flutter with spontaneous reversion to sinus tachycard. T-wave changes in chest leads typical of either pericarditis or myocarditis.	Pos.
(7) P.M. 570	2 cm. tumor nodule in left aur. and involvement of subepicard. lymphatics.	P pulmonal which later changed to auric. flutter. Last tracing taken 3 months prior to death.	Equivocal
(8) P.M. 610	Subepicard. lymphatic involvement with myocard. infiltration in both aur.	Auric. fibrill. with T-wave changes in chest leads typical of myocarditis and digitalis effect.	Pos.
(9) P.M. 640	Obliteration of pericard. sac by adhesions and tumor tissue.	Rhythm fluctuating from sinus tachycard. to auric. fibrill. ST and T-wave changes typical of pericarditis.	Pos.
(10) P.M. 721	Extension of tumor tissue down great vessels with invasion of pericard. at base of heart and seeding of epicard.	Sinus tachycard. in tracing taken 1 month before death.	Neg.
(11) P.M. 757	Pericard. sac obliterated by adhesions and tumor tissue. Nodules present in myocard. of both ventricles.	Rhythm varying between sinus tachycard., auric. fibrill. and auric. flutter. Varying degrees of A-V block.	Pos.
(12) P.M. 902	Pericard. sac obliterated by fibrous adhesions and tumor tissue.	Low voltage. Changes typical of pericarditis.	Pos.
(13) P.M. 1046	Serosanguineous pericard. exudate with multiple small white tumor nodules scattered over parietal and visceral pericard. with early myocard. invasion.	Sinus tachycard. Low voltage. Changes typical of pericarditis.	Pos.

(*continued*)

TABLE 3.—*Continued*

Case	Anatomic Findings	Electrocardiographic Changes	Correlation
	Bronchogenic Carcinoma—Continued		
(14) P.M. 1135	Sanguineous pericard. effusion. Subepicard. lymphatics filled with tumor tissue with early invasion of outer layer of myocard.	Sinus tachycard., nodal premature systoles with short P-R interval and prolonged QRS complexes.	Pos.
(15) P.M. 1307	Involvement of subepicard. lymphatics by tumor tissue.	Low voltage with a small Q wave and inverted T wave present in aV_1. Last tracing taken 24 days before death.	Equivocal
(16) P.M. 1349	Pericard. sac obliterated by 2 cm. thick layer of tumor tissue. Subepicard. lymphatics filled with tumor tissue with early myocard. invasion.	Low voltage. Changes typical of chronic pericarditis.	Pos.
	Malignant Melanoma		
(1) P.M. 121	Parietal and visceral pericard. contain numerous tumor nodules. Numerous nodules scattered throughout myocard. of all 4 heart chambers.	Low voltage. Tracing suggests myocardial disease.	Pos.
	Malignant Lymphoma		
(1) P.M. 216	Serosanguineous pericard. effusion. Subepicard. lymphatics contain tumor tissue (lymphocytic lymphosarcoma).	Low voltage. Sinus tachycard. Tracing consistent with early pericarditis.	Pos.
(2) P.M. 269	Scattered gray nodules in subepicard. region. (Hodgkins)	Sinus tachycard. Low voltage. Changes typical of chronic pericarditis.	Pos.
(3) P.M. 806	Pericard. sac obliterated by sheet of tumor tissue (reticulum cell sarcoma).	Sinus tachycard. Tracing typical of chronic pericarditis.	Pos.
	Carcinoma of Pancreas		
(1) P.M. 1095	Serosanguineous pericard. effusion. Epicard. surface covered by fibrinous exudate. Subepicard. lymphatics filled with tumor tissue with early myocard. invasion.	Sinus tachycard. Low voltage. Changes typical of chronic pericarditis.	Pos.
	Carcinoma of Kidney		
(1) P.M. 529	Pericard. sac obliterated by adhesions and tumor tissue. Tumor nodules present in epicard.	Auric. fibrill. with ventric. premature systoles arising in left ventricle.	Pos.
	Carcinoma of Prostate		
(1) P.M. 1075	Scattered small microscopic tumor nodules in myocard. Mild left ventric. hypertrophy.	Low voltage. Left ventric. hypertrophy pattern which reverted to normal just prior to death. Last tracing taken 27 days before death.	Equivocal

Malignant Lymphoma

In this series of tumor deaths, there were 60 cases with malignant lymphoma. Twelve had lymphosarcoma, and five of these showed myocardial involvement (see fig. 4). In one case the pericardial sac was obliterated, and the electrocardiogram showed low voltage, sinus tachycardia and changes consistent with pericarditis. In two other cases there was a serosanguineous pericardial effusion. The heart weight was increased in one case. There was epicardial spread in four cases and myocardial nodules in one case. The mediastinum contained tumor in three cases.

Two of seven cases of reticulum cell sarcoma had epicardial tumor, and in both the mediastinum was involved. The pericardial sac was obliterated in one case, and an electrocardiogram showed sinus tachycardia and changes typical of chronic pericarditis.

Of 39 cases of Hodgkin's disease, only two disclosed heart metastases. In both the epicardial layer was involved. An electrocardiogram in one case showed sinus tachycardia, low voltage, and changes consistent with pericarditis. Mediastinal involvement was present in both cases.

Two cases of mycosis fungoides had no cardiac metastases.

Carcinoma of Pancreas

Seven of the 33 cases of carcinoma of the pancreas had cardiac metastases. Four of these followed lymphatic pathways and involved the subepicardial region, while two showed myocardial nodules and one had implants only between the trabeculae of the right ventricle. In four cases there was pericardial effusion, and in one of these, the effusion was serosanguineous. The electrocardiogram of the last mentioned case disclosed sinus tachycardia, low voltage, and changes typical of chronic pericarditis. Mediastinal involvement was noted in three cases.

Carcinoma of the Esophagus

Six of the 33 cases in this group had cardiac involvement, and one of these showed direct extension through the pericardium. In four there was subepicardial and mediastinal involvement, and in two the metastases were blood-borne. In three instances there was pericardial effusion, one being sanguineous. One case disclosed obliteration of the pericardial sac by tumor tissue. No electrocardiograms were taken.

Carcinoma of the Kidney

Four of 15 cases in this group had cardiac metastases. Epicardial and mediastinal involvement was present in three instances, while the fourth case had endocardial implants attached to the papillary bundles of the right ventricle. The pericardial sac was obliterated by tumor in one case, and an electrocardiogram disclosed auricular fibrillation and ventricular premature systoles.

Testicular Tumors

Four of nine testicular tumors metastasized to the heart, three via the blood stream and one through lymphatic channels (see fig. 5). In one case there was bloody pericardial effusion. No electrocardiograms were taken.

Other Tumors

In both cases of carcinoma of the stomach the metastases were blood-borne. One case of prostatic carcinoma had hematogenous metastases, while in the other they were lymphatic. In the cases with carcinoma of the bladder and adrenal gland the metastases were via lymphatics, and both cases showed pericardial effusion. The other cases had hematogenous metastases, and none had significant pericardial effusion.

Discussion

The symptoms most frequently listed in cases with heart metastases are tachycardia, dyspnea, cough, cyanosis, precordial pain, arrhythmias, and edema of the lower extremities. Symptoms alone are not diagnostic of myocardial metastasis.

Clinically, the patient with cardiac metastases may exhibit a number of findings suggesting the diagnosis. In addition to the

irregularities of rhythm mentioned above, there may be a pericardial friction rub, heart failure refractory to treatment, pericardial effusion which is often bloody, diminished heart sounds, and falling blood pressure. An occasional case may show the findings of chronic constrictive pericarditis,[12-16] and rarely there may be sudden death.

The roentgenographic and fluoroscopic changes may be helpful. These include large heart shadow, findings of pericardial effusion, and fixation of a border of the heart. These changes have been given attention in the following reports.[3, 4, 5, 7, 17]

As stressed by Yater,[3] the onset of cardiac symptoms or findings of cardiac disease without apparent cause in a patient with known malignancy is highly suggestive of cardiac involvement by tumor.

Electrocardiographic changes in cases with heart metastases have received much attention in the literature. Fishberg,[18] who was the first in America to report cases of cardiac metastases diagnosed during life, in 1930 noted auricular fibrillation and flutter in his three cases, while Willius and Amberg[19] also in 1930 reported a case diagnosed during life in which the electrocardiogram disclosed incomplete bundle branch block, low amplitude, and T-wave changes.

In 1933 Siegel and Young[20] reviewed much of the literature concerning electrocardiographic changes and felt that records in tumor cases gave some evidence as to the location of the heart metastases. Scott and Garvin[8] found auricular fibrillation and flutter and auricular premature contractions the commonest changes in their series. The commonly reported changes include sinus tachycardia, auricular fibrillation and flutter, auricular premature contractions, varying degrees of A-V dissociation, ventricular premature contractions, low voltage, and changes suggestive of myocardial or pericardial involvement, but these changes by themselves are not diagnostic.

The metastatic pathways taken by tumors reaching the heart are usually listed as the blood stream, lymphatics, and direct extension, the last being unusual since the pericardium is a strong barrier.

It is at times difficult to ascertain the exact route taken in myocardial involvement. When mediastinal involvement is marked, continuous retrograde lymphatic permeation can occur, or there may be retrograde lymphatic embolization. We have accepted isolated intramural nodules as hematogenous metastases, though it seems possible that some of these may have begun from small tumor emboli in perivascular myocardial lymphatics.

Willis[6] has classified involvement as arising from (a) direct nonmetastatic invasion from contiguous growths, via lymphatics, via the venae cavae, and via the pulmonary veins, and (b) true embolic metastasis by endocardial implantation and via the coronary arteries. Morris[2] in 1927 felt that the hematogenous route was the most common, but one must consider the tumor type when pathways are discussed. True endocardial implants represent an uncommon type of metastasis, and these are discussed by Willis,[6] Coller and associates,[21] Nicholls,[22] and Herbut and Maisell.[7] In our series, endocardial implants occurred in a case of carcinoma of the pancreas and a case of carcinoma of the kidney. Myocardial nodules may ulcerate through the endocardium and implant within the chambers. We noted this latter occurrence in single cases of malignant melanoma, bronchogenic carcinoma, and carcinoma of a paranasal sinus. Tumors which most frequently implant on the endocardium are those of the genitourinary tract, chiefly the testicular and kidney tumors, and those of the gastrointestinal tract. In this series no case of direct extension through the venae cavae was noted.

The supposed infrequency of cardiac metastases has been explained in several ways. Recently these were summarized by Prichard[1] as (a) the strong kneading action of the heart, (b) the metabolic peculiarities of striated muscle, (c) the rapid blood flow through the heart, and (d) the restricted lymphatic connections making retrograde lymphatic extension necessary. Another factor mentioned is that the coronary arteries arise from the aorta at right

angles. Actually, for types of tumors such as bronchogenic carcinoma, carcinoma of the breast, malignant melanoma, malignant lymphoma, and carcinoma of the pancreas and esophagus, cardiac metastases are relatively common.[1, 6-9, 23-26]

Bronchogenic carcinoma frequently involves the heart usually by way of the mediastinal lymphatics. This mode of spread has been stressed by Morris[2] and Willis.[6] As early as 1912 Adler[27] had noted frequent pericardial and cardiac involvement, and Simpson[28] in 1929 found 62 of 139 cases of bronchogenic carcinoma with pericardial invasion. A survey of many case reports emphasizes the frequent pericardial and epicardial involvement with effusion or obliteration of the pericardial space.

It has been estimated[29] that half the cases of malignant melanoma show cardiac metastases; these usually follow the hematogenous route and are extensive. Reviews emphasizing secondary melanoma in the heart[30, 31] show that few electrocardiographic tracings have been obtained. Certainly, many of these cases terminally should show significant changes in their tracings. The few changes reported are low voltage, sinus tachycardia, and findings suggesting myocardial involvement.

Of the malignant lymphomas, lymphocytic and lymphoblastic lymphosarcoma most frequently involve the heart,[7, 32, 33] and this was particularly prominent in our series. The method of extension may be lymphatic, infiltrative, or rarely hematogenous with formation of nodules. Epicardial and pericardial involvement with effusion is the usual finding. Reticulum cell sarcoma shows a somewhat less striking tendency for cardiac metastasis.[34, 35] Hodgkin's disease, on the other hand, even less frequently shows cardiac spread. Rottino and Hoffman[36] in 1952 reported five instances in a series of 63 cases. Herbut and Maisell[7] had 2 instances in 13 cases, while Lucia and coworkers[33] noted 3 cases in 18. Other articles concerning Hodgkin's disease with cardiac involvement are those of Harrell,[37] Garvin,[38] and Ritvo.[39]

In the malignant lymphomas the most significant involvement is usually in the epicardium and pericardium with effusion or obliteration of the sac, giving findings and electrocardiographic changes of pericarditis and even constrictive pericarditis.

Our cases of carcinoma of the pancreas and esophagus disclosed frequent epicardial and pericardial involvement, and more than half had notable pericardial effusion. This is in agreement with cases reported in the literature.

Observations and Conclusions

The diagnosis of secondary neoplastic spread to the heart offers a challenge to the clinician. If one is alert to this possibility, there are frequently symptoms, signs, and laboratory changes indicating the diagnosis, especially in the patient with known malignant disease. While such a diagnosis is usually of little importance in the patient's course, a few investigators[9, 38, 40, 41] have used pericardial aspiration and/or deep roentgen therapy with beneficial though temporary results. Roentgen therapy in these cases, particularly in malignant lymphoma and small cell bronchogenic carcinoma with cardiac spread, deserves further investigation. Pericardial aspiration may help establish the diagnosis if the fluid is examined for tumor cells.

The authors, after a survey of the literature and study of this series of tumor deaths, feel that the following observations are in order.

1. Malignant tumors, particularly bronchogenic carcinoma, malignant melanoma, malignant lymphoma, and carcinoma of the breast, pancreas, and esophagus, involve the heart secondarily with relative frequency.

2. The diagnosis of cardiac spread in these cases can often be made by the alert clinician who makes use of the symptoms, signs, electrocardiographic and roentgen changes often present.

3. While there are no electrocardiographic changes pathognomonic of cardiac metastasis, certain changes do occur, and these show fairly close correlation with the anatomic changes present.

4. Deep roentgen therapy deserves further

study as a means of relieving the embarrassed heart.

Summary

A large series of tumor deaths was studied for cardiac metastases in a Veterans Administration hospital. The incidence of cardiac metastasis in this somewhat selected group was 19.1 per cent. The bulk of the cases were bronchogenic carcinoma, malignant melanoma, malignant lymphoma, and carcinoma of the pancreas and esophagus. Correlation of electrocardiographic changes and anatomic findings is given. Likewise, the behavior of the individual types of tumors with reference to pathologic findings is presented.

Sumario Español

Este artículo es un repaso de 476 casos consecutivos de muertes debido a envolvimiento del corazón por tumor. Este grupo de casos algo seleccionado (de un Hospital de la Administración de Veteranos) muestra una incidencia de metástasis cardíaca de 19.1 por ciento. El volumen de tumores con metástasis al corazón fueron los carcinomas bronquiogénicos, melanoma maligno, linforma maligno, y carcinoma del pancreas y el esófago. Cambios electrocardiográficos fueron frecuentes y correlacionaron bastante cercanamente con la extensión anatómica de la enfermedad. La literatura relacionada se repasa.

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Clinical Experience with a New Anticoagulant, Dipaxin (2-diphenylacetyl-1,3-indandione)

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Prothrombin levels as measured by the one-stage whole-plasma and the two-stage technics were followed in 80 patients receiving Dipaxin. The induction period is similar to that for Tromexan, namely, 48 to 60 hours and the recovery period 10 to 15 days which is somewhat longer than in the case of either Tromexan or Dicumarol. This recovery period is hastened to some degree by the administration of water-soluble vitamin K preparations and materially accelerated by vitamin K_1. The prothrombin level during maintenance therapy is unusually stable. Transient bleeding occurred in two patients. No other toxic effects were observed.

THE prevention of intravascular clotting has become of prime importance in the treatment of certain diseases. In a search for the ideal orally administered anticoagulant, numerous substances are being studied experimentally.[1, 2, 3] In contrast, the clinical use of oral anticoagulants has been practically limited to the derivatives of coumarin (Dicumarol and Tromexan). Derivatives of 1,3 indandione have been receiving increasing clinical application.[4, 5] The hypoprothrombinemic effect of these substances was demonstrated in animals as early as 1944 by Kabat and associates,[1] but since that time only a few reports of the clinical use of such drugs have been described. Of them, phenylindandione has received the greatest attention.

Correll[2] studied numerous derivatives of 1,3-indandione experimentally, the most potent of them being 2-diphenylacetyl-1,3-indandione (Dipaxin). In a comparative experimental study of this drug with Dicumarol and Tromexan, Dipaxin was found to be 200 times as potent as Dicumarol and 1000 times stronger than Tromexan. It was also found to have an induction period as short as that of Tromexan and to have the sustained hypoprothrombinemic effect of Dicumarol. Vitamin K_1 was found to be an adequate antidote against the Dipaxin induced prothrombinopenia. Recently Field, Goldfarb, Ware and Griffith[6] reported satisfactory lowering of the prothrombin in control patients and those having evidence of intravascular clotting. They observed no toxic effects in the approximately 110 cases observed. The purpose of this paper is to report our experience with the use of Dipaxin in 80 patients.

From the Surgical Service of the Presbyterian Hospital of the City of Chicago and the Hektoen Institute for Medical Research, Cook County Hospital, Chicago, Ill. This study was supported in part by grants from the Otho S. A. Sprague Memorial Institute Fund, the Arthur Dean Bevan and Anna L. Bevan Funds, and the Upjohn Company.

METHODS

Blood prothrombin levels were determined in all patients by the two-stage method of Warner, Brinkhous and Smith[7] as modified by Ware and Seegers.[8] In each instance a one-stage determination was also carried out, the original technic of Quick[9] being followed with the exception that Soluplastin* was used as thromboplastin in place of rabbit brain extract. In our hands this has been found to be quite stable and yields relative uniform curves from lot to lot. In the following pages wherever prothrombin or prothrombin level is mentioned without specific designation of the one-stage or two-stage technic the latter will be understood. This method is used routinely in our laboratory for the control of all prothrombin depressants.[10-12]

The effect of Dipaxin† was studied on 80 patients from the wards of the Presbyterian and the Cook County Hospitals. Until after the completion of this study we had no information on the use of the drug in human beings, and it was deemed necessary to proceed with caution. It was also considered important to observe the effect of a single dose of the drug from the point of view of the induction period, the degree of hypoprothrombinemia produced and the length of time such an effect was maintained. Accordingly, 30 patients received single doses of

* Kindly supplied by Dr. E. W. Blanchard of Scheifflin & Co.

† Kindly furnished by Dr. H. F. Hailman of the Upjohn Co.

Dipaxin varying from 1 to 25 mg. (Two patients were given 1 mg. each; two were given 1.5 mg.; five patients were given 3 mg.; three patients were given 4 mg.; five patients were given 5 mg.; two patients were given 8 mg.; one was given 10 mg.; four patients were given 12 mg.; four patients were given 15 mg.; and two patients were given 25 mg. each.) The prothrombin levels were measured daily or every second day for from 5 to 18 days following the administration of the drug.

In order to determine the safety of repeated doses of the drug five patients were given Dipaxin intermittently and observed for cumulative effects. Doses of Dipaxin were given at two to four day intervals.

The remaining 45 patients were given initial doses of 15, 20 and 25 mg. and subsequent daily doses to attain a therapeutic level as rapidly as possible. These patients were maintained on the drug for periods of time varying from 4 to 162 days. Twenty-seven were on the drug for at least two weeks, 20 for three weeks, 11 for four weeks, 7 for five weeks, 5 for six weeks and 2 patients for over eight weeks. One patient took the drug for over five months. Three of the 45 patients were followed, during part of their course, as out patients. Prothrombin levels were measured usually daily for the first two weeks then every two to five days subsequently. The one long-term case eventually reported for examination at two-week intervals. There were 12 patients in the maintenance therapy group who were allowed to recover spontaneously and were followed for 3 to 21 days after withdrawal of the drug.

In five patients who received Dipaxin for a minimum of three weeks the following liver function tests were done at the end of the administration of the drug: cephalin flocculation, thymol turbidity, gamma globulin, cholesterol, alkaline phosphatase, total protein and icterus index.

Seven patients were given 72 mg. of Hykinone intravenously (24 mg. in each of three injections at 30-minute intervals) 24 hours after the last dose of the drug. Two additional patients were given 288 mg. of Hykinone intravenously over a two-hour period. One patient with a prothrombin of 4 per cent and bleeding from the gastrointestinal tract was given 50 mg. of Hykinone intravenously daily for three days in addition to 500 cc. of whole blood. Another patient, in order that surgery might be safely carried out, was given intravenous doses of 72, 50 and 50 mg. of Hykinone, respectively, on successive days. Three patients were given 500 mg. of K-analogue* intravenously over a two-hour period. Varying doses of vitamin K_1 (Mephyton)† were given to six patients who had been maintained on Dipaxin for less than two weeks. Three of these patients received the drug orally in doses of 50, 100 and 150 mg. respectively. Two patients were given K_1 intravenously by infusion over a two-hour period, one receiving 50 mg. the other 100 mg. The sixth patient, who had gross hematuria, was given 50 mg. orally and 100 mg. intravenously on the same day.

In an effort to compare the effects of certain of the prothrombin depressing drugs in the same patient, seven patients were given successive courses of Dipaxin, Tromexan and Dicumarol after sufficient time had elapsed for the prothrombin level to return to normal following withdrawal of each drug.

Results

Effects of Single Doses of Dipaxin. Those patients who received 1 or 1.5 mg. of Dipaxin showed no significant change in their prothrombin level. Five patients who were given a single dose of 3 mg. showed a distinct lowering, (fig. 1*A*), the average decrease in prothrombin percentage being 34 per cent as measured by the two-stage test and 28 per cent by the one-stage. The lowest level (63 per cent) was observed at approximately 36 to 40 hours after the administration of the drug. The depression measured by the two-stage method was sustained for two days and then returned to the pretreatment levels. The composite effects of 5 mg. dosages of Dipaxin are seen in figure 1*B*. The drop in prothrombin level was less than 10 per cent as measured by both the two-stage and one-stage prothrombin tests. In the three patients who were given either 8 or 10 mg. the drop in the two-stage prothrombin level was 35 to 44 per cent and the one-stage prothrombin level fell from 24 to 51 per cent. These drops (to levels as low as 48 per cent) occurred within the first 40 hours following the ingestion of the drug. The average effect on the prothrombin level in four patients given 12 mg. of Dipaxin is shown in figure 1*C*. The depression was 41 per cent as measured by the two-stage and 24 per cent by the one-stage test. The most rapid lowering came in the first 24 hours and the prothrombin continued to fall during the next two days. Unlike the change in the instances of the lower doses where a rather prompt rise occurred after the nadir, these patients maintained a lowered prothrombin level for longer than the seven days. The effect of a single dose of 15 mg. of Dipaxin on four patients is seen in figure 1*D*. The composite of

* Kindly supplied by Dr. H. F. Hailman of the Upjohn Co.

† Courtesy of Dr. R. C. Major of Merck and Co.

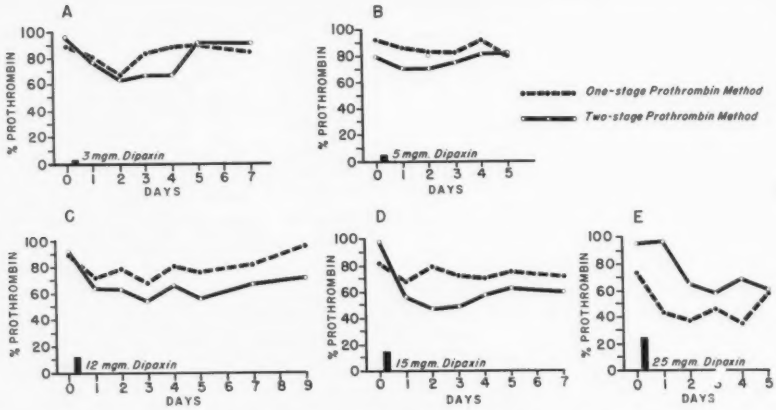

FIG. 1. The above group of graphs represents the effects of varying single doses of Dipaxin on the prothrombin levels (two-stage) of human beings. (*A*) This chart shows the composite response of five patients who received 3 mg. each. As measured by the one-stage test there was a drop of 28 per cent and by the two-stage a drop of 34 per cent (to 63 per cent) in 36 hours. (*B*) Strangely enough, the five patients who were each given 5 mg. of Dipaxin showed less of a prothrombin depression than those given 3 mg. each, 10 per cent being the average drop. (*C*) The four patients receiving 12 mg. each showed an average lowering of 41 per cent, the greatest drop occurring in the first 24 hours and the fall continuing for the next two days. Unlike the change in the instances of the lower doses, where a rather prompt rise occurred after the nadir, these patients maintained a lowered level for longer than seven days. (*D*) The four patients who were given 15 mg. each showed an average drop of 51 per cent, the lowest level of 47 per cent occurring in about 40 hours. As in the case of the 12 mg. dose, the prothrombin remained depressed over the seven-day observed period. (*E*) The two patients receiving 25 mg. each showed a maximum average drop of 39 per cent the lowest level (35 per cent) being reached in 40 hours.

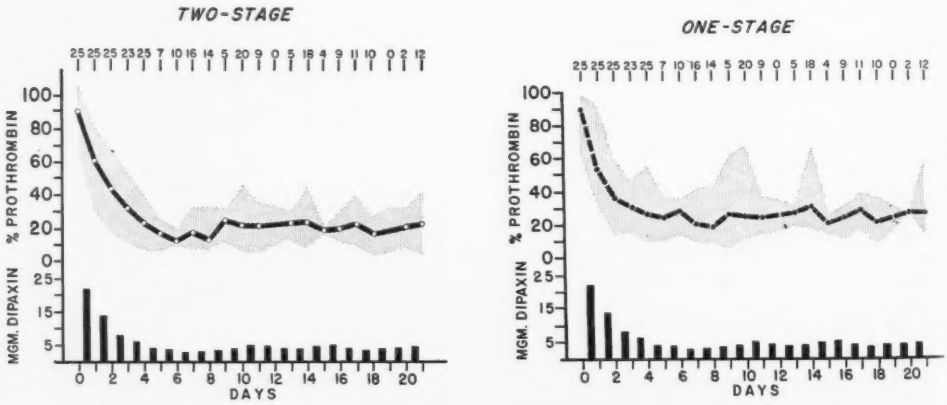

FIG. 2. The above graphs represent the composite course of 25 patients who were maintained on continuous Dipaxin therapy for a minimum of three weeks. The chart on the left shows the prothrombin levels as measured by the two-stage test and on the right the corresponding one-stage levels are shown. The heavy line in each graph indicates the average course and the shaded area the limits of individual determinations on respective days. Note that the prothrombin as shown by the one-stage test drops more promptly than that measured by the two-stage and then returns to and remains at a higher level throughout the course of the therapy. There were also wider variations in the one-stage estimations than in the two-stage.

th prothrombin percentages of these patients re eals an overall drop of 51 per cent in the tv o-stage and 15 per cent in the one-stage de- te minations. The prothrombin level remained d pressed over the observed period of seven d ys. The change in the prothrombin percent- a e in two patients after receiving 25 mg. of I ipaxin orally is seen in figure 1*E*. In these p tients there was a maximum drop in the pro- t rombin level of 39 per cent in the two-stage a d 40 per cent in the one-stage test, the great- e t fall being in the first 40 hours with a further decrease in prothrombin level over the next two days.

Maintained Dipaxin Therapy. Twenty patients had initial doses of 20 mg. and 22 patients received 25 mg. In three patients with prothrombin percentages in the 70's both by the two-stage and one-stage prothrombin tests, the initial dose of Dipaxin was 15 mg. Subsequent dosage was dictated by the change in the two-stage prothrombin level. If the prothrombin percentage was between 50 and 80 per cent, 15 mg. were given, if it was between 35 and 50 per cent, 10 mg. and if the prothrombin was 20 to 35 per cent, 5 mg. of Dipaxin were administered; when the prothrombin levels were 15 to 20 per cent, 1 to 3 mg. of the drug were given. If during the induction period the prothrombin level fell rapidly to below 30 per cent the drug was withheld or a very small dose was given (1 to 2 mg.). This modification of dosage scheme was followed also during maintenance therapy whenever there was a rapid drop in the prothrombin percentage. The course of 25 patients over a three-week period is summarized in composite graphs shown in figure 2. The therapeutic prothrombin level was attained in an average of 60 hours the range being 40 to 96 hours. The lowest levels usually occurred between the sixth and eighth days. After the initial administration of the drug the average doses for the second, third and fourth day decreased progressively to 14, 8 and 6 mg. The maintained dose was, on the average, 3 to 5 mg. daily, the range being 0 to 7 mg.

The one-stage level in the early period (first two to three days) dropped more rapidly than the two-stage level, after which the latter was, for the most part, slightly lower than the one-stage throughout. This is comparable to the observed behavior of the two tests in patients given Dicumarol[11] or Tromexan.[13] Following the withdrawal of the drug there was a very slow rise in the prothrombin level, the return to normal or near normal requiring 15 to 20 days.

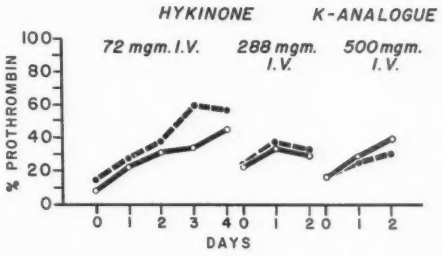

FIG. 3. This chart shows the effect of two of the water-soluble vitamin K preparations on the prothrombin levels (two-stage) of patients on maintained Dipaxin therapy. The lines on the left represent a composite of the responses of seven patients with prothrombin levels below the lower limit of the therapeutic bracket. Each patient received 72 mg. of Hykinone intravenously (24 mg. in each of three injections at 30-minute intervals) 24 hours after the last dose of the drug.

The pair of lines in the center represents the course of two patients who received 288 mg. each of Hykinone in divided doses over a two-hour period. They were within the therapeutic bracket when the drug was given. The prothrombin rose from 24 to 34 per cent in 24 hours and dropped to 29 per cent at the end of 48 hours.

The third pair of lines shows the responses of three patients to 500 mg. of K-analogue given in divided doses over a two-hour period. They were similar in character to those of the patients receiving 72 mg. of Hykinone.

In contrast to this is seen the more rapid increase in the prothrombin level following the administration of vitamin K derivatives. The summation of the prothrombin levels of the seven patients who received 72 mg. of Hykinone is shown in figure 3. The prothrombin level is seen to increase steadily during the following four days. These patients had an average prothrombin that was below the lower limit of the therapeutic bracket, and within 16 hours the average level of the prothrombin had increased to the therapeutic range. The two patients who received 288 mg. of Hykinone by intravenous infusion were within the thera-

peutic bracket, and their response is also shown in figure 3. The prothrombin rose from 24 to 34 per cent in 24 hours and dropped to 29 per cent at the end of 48 hours.

The effect of the intravenous administration of 500 mg. of K-analogue on induced hypoprothrombinemia in three patients is also shown in figure 3. The prothrombin level was followed for two days and showed an increase similar to that seen following the administration of 72 mg. of Hykinone.

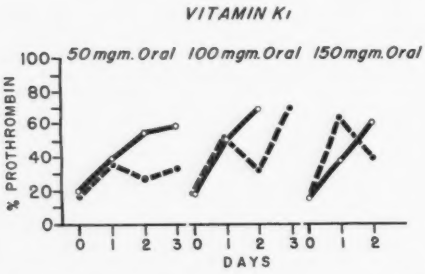

FIG. 4. The above graphs show the response of individual patients on maintained Dipaxin therapy to single oral doses of vitamin K_1. Each patient had been on the drug for eight days. The first had received a total of 68 mg. of Dipaxin, the second 85 mg. and the third 76 mg. All were within the therapeutic bracket when the vitamin K_1 was given and all showed a prompt rise of approximately 20 to 30 per cent in 24 hours.

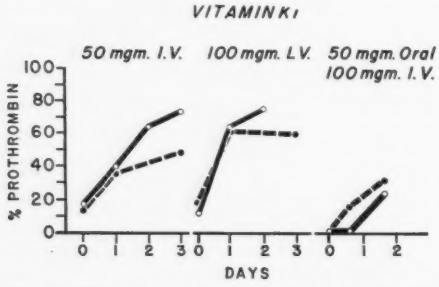

FIG. 5. This chart shows the effect of vitamin K_1 given intravenously to patients with Dipaxin produced hypoprothrombinemia. The responses are similar to those occurring when the vitamin was given orally, though the 24-hour rise in the case of the patient receiving 100 mg. intravenously was considerably greater than in patients getting the drug orally. The pair of lines on the right shows the response of a patient to combined oral and intravenous vitamin K_1. This patient had hematuria and lumbar pain when the drug was given and her prothrombin was less than 1 per cent of normal. The pain and bleeding stopped 15 hours after the vitamin was given. The first patient had been given 61 mg. of Dipaxin in eight days, the second 49 mg. in six days and the patient with the hematuria had received 190 mg. over a period of 35 days.

Vitamin K_1 brought about the most rapid rate of recovery in the prothrombin level. In the few cases observed the drug (fig. 4) appeared to be slightly less effective when given orally than when administered by the intravenous route (fig. 5). In one patient who received 100 mg. of vitamin K_1 intravenously the prothrombin rose from 12 to 64 per cent within 20 hours (fig. 5).

Comparison of Dipaxin, Tromexan and Dicumarol

The composite responses of seven patients each receiving Dipaxin, Tromexan and Dicumarol successively and in that order are shown in figure 6. The rate of induction of the prothrombinopenic levels are similar for Dipaxin and Tromexan. The therapeutic level was attained with these drugs in approximately 60 hours. In the case of Dicumarol the therapeutic level had not quite been reached at the end of 96 hours. One patient was more resistant than the other six. Higher doses of Dipaxin and Tromexan than usual were necessary adequately to suppress the prothrombin level.

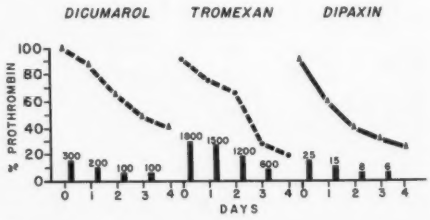

FIG. 6. The above graphs represent the composite responses of seven patients who were given successive courses of Dipaxin, Tromexan and Dicumarol, sufficient time being allowed between courses for the prothrombin levels to return to normal. In the case of Tromexan and Dipaxin the the therapeutic level was reached between 48 and 72 hours after the drug was started. The average prothrombin level of the patients when receiving Dicumarol had not quite reached the therapeutic bracket 96 hours after the drug was started. All points represent two-stage prothrombin levels.

Even large doses of Dicumarol did not effect an adequate decrease in the prothrombin level after one week.

Toxicity

The liver function tests carried out on five patients who received Dipaxin for a minimum of three weeks showed no significant variations from the normal. No untoward clinical signs or symptoms other than bleeding were observed in any of the patients taking Dipaxin.

Discussion

The criteria for the evaluation of any prothrombin depressant are safety, effectiveness, economy and convenience in descending order of importance. No drug available at the present time meets these requirements satisfactorily. From the foregoing data, Dipaxin would appear to fulfill them to an extent similar to that of its predecessors. Of the drugs used clinically to date, it is the most potent, hence the required dosage is the lowest. The induction rate is similar to that of Tromexan and shorter than that of Dicumarol. Patients receiving it are readily controlled within the therapeutic prothrombin bracket and are easily maintained within that bracket over a period of time. Once the therapeutic level is achieved the prothrombin is reasonably stable, more so, in our experience, than in the case of patients receiving Dicumarol or Tromexan. This, no doubt, is related to the character of the recovery period which is somewhat longer than that of Dicumarol-treated patients. It is considerably longer than that of Tromexan, the latter requiring 24 to 48 hours while most patients receiving Dipaxin did not show a near normal prothrombin until 15 to 20 days following withdrawal of the drug. The recovery period in patients receiving Dicumarol is about one-half that time. This is both an advantage and disadvantage. It insures a steadily controlled patient despite an occasional accidental omission of the daily dose. It has the disadvantage of a slow recovery when a rapid return towards normal is desired for unexpected surgery, in the case of injury or when an unusually low prothrombin level and bleeding occur. This slow recovery period is in all probability also related to the relative ineffectiveness of the standard vitamin K preparations in counteracting the prothrombinopenic action of the drug. And these three characteristic effects of the drug—stable therapeutic prothrombin bracket, slow recovery period and resistance to standard vitamin K active substances—are undoubtedly based on a cumulative action greater than that of the two other drugs. The rapid action of vitamin K_1 in neutralizing the effects of the drug insures its safety.

The incidence of bleeding in our series (slightly more than 2 per cent) was less than that which we have observed with Tromexan and Dicumarol. There have been fewer patients whose prothrombin levels were below the therapeutic bracket for any period of time, and this may be the sole reason for the lowered incidence of hemorrhage. It is also possible that other factors such as capillary fragility are less altered. The one patient in whom bleeding was definitely attributed to the effect of Dipaxin responded promptly to vitamin K_1, and the hematuria and symptoms disappeared within 24 hours after the vitamin was given.

From our study, the possibility of hemorrhage would appear to be the only hazard in the administration of the drug. There were no other apparent toxic effects, subjectively or objectively. Except for an occasional complaint of nausea with a large dose the same may be said of Dicumarol. Dermatitis which has occasionally accompanied the use of Tromexan[13] has not been observed with Dicumarol or Dipaxin. As a result of our early studies on Dicumarol we have used the two-stage prothrombin assay routinely for the control of prothrombin depressants. While it is a more complicated procedure, it reflects, we believe, a more accurate prothrombin level and hence provides a more safely controlled patient from the points of view of both clotting and bleeding. Inasmuch as the one-stage method is a less complicated test and is more widely used, we believe that it should be evaluated in connection with each prothrombin depressant studied. Modifications of the one-stage test from time to time may alter its relationship to the two-stage test and to anticoagulant ther-

apy in general, a point of particular importance in the control of any prothrombin depressant.

In previous studies on Dicumarol we have found the results of the one-stage technique in some patients to vary widely from those of the two-stage.[10-12] A recent survey of our data covering the use of Dicumarol in patients in whom both tests were run in parallel showed this to be true in approximately 73 per cent of the cases.* In a recently completed study on Tromexan 51 per cent of 116 patients showed such a variation.[13] It was true of Dipaxin in 32 per cent of the 80 patients studied. From this point of view, Dipaxin would appear to be a safer drug. The possible causes of such variation have been discussed in earlier communications and will not be taken up here. They are still poorly understood. As in the case of the other drugs[11, 13] levels determined by the one-stage method show an earlier drop than those found by the two-stage and after the first few days assume a position 10 to 20 points above the level of the two-stage method.

The results of Field, Goldfarb, Ware and Griffith[6] are similar to those recorded here with the following notable exceptions: (1) In our experience the return of the prothrombin to normal after the withdrawal of Dipaxin is considerably longer than that observed in their patients (15 to 20 days as compared with 3 to 6). (2) In our series water-soluble vitamin K active substances only slightly affected the hypoprothrombinemia produced by Dipaxin; this is in accord with the findings of Correll and coworkers.[2] The disparity in the first instance is not clear. The difference in the responses to water-soluble vitamin K preparations may result from the fact that our cases had had repeated doses of Dipaxin and only one day of vitamin K dosage, whereas the cases of Field and coworkers received a single dose of Dipaxin and vitamin K over a number of successive days. They also administered the vitamin intramuscularly whereas our patients received it intravenously. In their discussion they note that the induction period is greater than that of Dicumarol, a finding contrary to ours though the actual time observed, 48 to 60 hours, is very similar to that seen in our patients. In our experience Dicumarol requires a longer period to produce its maximum effect.

We have had insufficient experience with Cumopyron and phenylindandione to compare them with Dipaxin, Tromexan and Dicumarol.

As yet we have had little experience with the use of Dipaxin in patients with thromboembolism. Since, however, it is effective in controlling the prothrombin level in a uniform and safe manner one would expect it to be a satisfactory drug for the treatment of such conditions.

* In most of these instances acetone-dried rabbit brain was used as the thromboplastin. In a small number of cases in which Soluplastin has been employed it has been our impression that this has been present to a lower degree.

Summary

1. The drug 2-diphenylacetyl-1,3-indandione (Dipaxin) has been used to reduce the prothrombin level in 80 patients, most of them suffering from conditions other than thromboembolism.

2. It is an effective prothrombin depressant, serving to reduce that coagulation factor to a therapeutic level in 48 to 60 hours and to maintain such a level uniformly over a period of weeks.

3. The recovery period after the withdrawal of the drug is 15 to 20 days, somewhat longer than that following Tromexan or Dicumarol.

4. This recovery is hastened to some degree by the administration of the standard vitamin K preparations and materially accelerated by vitamin K_1.

5. Bleeding occurred in two patients, an incidence of slightly more than 2 per cent. In the one patient in whom it could definitely be attributed to the lowered prothrombin the hematuria ceased within 24 hours after vitamin K_1 oxide was administered, the prothrombin returning towards normal during that period of time. There were no other toxic effects observed.

6. As in patients receiving Dicumarol or Tromexan variations between the prothrombin levels as measured by the one-stage and two-stage tests were present to a significant degree. The implications of these variations are discussed.

Sumario Español

Niveles de protrombina determinados por las técnicas de una etapa en plasma íntegra y de dos etapas fueron determinados en 80 pacientes que se les administraba "dipaxin." El período de inducción es similar al de "tromexan," o sea, 48 a 60 horas y un período de recuperación de 10 a 15 días el cual es algo mas largo que el de "tromexan" o dicumarol. Este período de recobro es aligerado en algún grado por la administración de preparaciones aquosolubles de vitamina K y materialmente acelerado por vitamina K_1. El nivel de protrombina durante la terapia sostenida es remarcablemente estable. Sangrías transitorias ocurrieron en dos pacientes. Ningún otro efecto tóxico fué observado.

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Sympathetic Denervation in the Treatment of Acute Arterial Occlusion

By JACK FLASHER, M.D., ALBERT E. WHITE, M.S., AND DOUGLAS R. DRURY, M.D.

The effect of sympathectomy on the size of the collateral vessels in acute arterial ligation in a hind limb was measured by an angiographic angiometric technic and by noting the pressure in the ligated artery distal to the ligature. The size of the largest collateral vessel present on the sympathectomized side was the same as that on the innervated side. The blood pressure in the ligated artery distal to the ligature was quite similar on the sympathectomized and innervated sides. The usual increase in temperature on the sympathectomized side was noted. This must be due to a shift of blood from the deeper tissues of the hind limb to the arteriovenous shunts of the skin of the toes, rather than to an increase in collateral blood flow.

THERE is still no general agreement as to which of the therapies available for the treatment of acute arterial occlusion in man are most important for limb and patient survival.[1-5] One of the major disagreements concerns the advisability of sympathetic blocks or sympathectomy in the early hours after acute occlusion.[1, 6, 7, 8] It is well established that sympathetic block or denervation, and similarly body heating, can increase total blood flow through the toes in the presence of arterial occlusion.[1, 9-13] Total blood flow includes the temperature-regulating arteriovenous shunt flow and the nutritional flow. It is often implied, however, that dilatation of the collateral arterial vessels in the early hours after acute arterial occlusion can be produced by sympathetic block but not by reflex heat.[1, 14] If it can be substantiated, this is certainly an important difference in favor of sympathetic block.

The use of sympathetic block, however, does entail some known disadvantages. There is a slight risk of hemorrhage, since immediate heparinization is almost always advisable in acute arterial occlusion. The patients are frequently quite ill[5] and do not readily tolerate the manipulation and exposure that is often involved in the usual performance of a sympathetic block. The evaluation of the degree of progression or regression of ischemia is an important factor in determining the need for embolectomy.[5] The close observation of the limb required in making a decision in regard to the latter may be interfered with during the execution of the block. Also, if the sympathetic chain is not successfully blocked, further cooling of the limb often ensues. This would appear to be detrimental. If, however, it can be shown that sympathetic block or sympathectomy can dilate the collaterals to a therapeutically significant degree, and simpler therapy cannot, the drawbacks associated with sympathetic block listed above would be minor deterrents. The evidence in this regard as applied to man is controversial.[6, 7, 15]

It is important to recall that the collaterals apparently open up spontaneously with the passage of time after acute occlusion. While observing a limb that has just suffered an acute occlusion, one not infrequently notes—usually within several hours, and occasionally up to 24 hours or so—a more or less rapid disappearance of the signs and symptoms of tissue ischemia.[5, 16, 17] In clinical experiments using alternate patients as controls, if one could show that soon after sympathetic block one obtained not only an elevation of skin temperature of the acral parts, but also a return of sensation and motion toward normal, one could conclude that sympathetic block is indeed important in the treatment, and that

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the effect was probably due to dilatation of collateral vessels. We think the latter presumption would be justified by the knowledge that any ischemia great enough to produce loss of motion and sensation of the acral parts must represent a marked impairment of inflow. Opening the "faucets" at the end of the line above that normally existing, and probably augmented by the ischemia, would probably not result in an increase of blood flow. Since such experiments in man have not as yet been done because of the inherent complexities, one might try to draw inferences from conclusions obtained from animal work.

In the dog, it is claimed that sympathectomy does increase collateral flow in acute arterial occlusion. Mulvihill and Harvey[11] found that following external iliac artery ligation the skin temperature of the paw (normally over 90 F. in the anesthetized dog) dropped rather rapidly toward room temperature, and after several hours it spontaneously started rising toward that of the control hind paw, so that in 12 hours or so both hind paws were again at the same temperature. Sympathetic denervation of the involved limb, performed before the arterial ligation, prevented the drop in temperature, and denervation performed after the temperature drop had occurred rapidly returned the temperature of the involved paw to that of the control paw. These authors surmized that this was evidence in favor of a salutory effect of sympathectomy on the collateral vessels. This may, however, represent an effect primarily on the temperature-regulating peripheral arteriovenous shunts in the presence of a normal collateral flow and may involve a concomitant reduction in blood flow through the deeper tissues, such as the muscles.

Theis,[18] however, has presented more direct evidence that sympathectomy can bring about dilatation of collateral vessels in acute arterial occlusion. He mentions four dogs in which he measured the pressure in the femoral artery distal to an acute occlusion (ligature)—the tip of the cannula pointing peripherally—with sympathetic denervation of one limb and without denervation of the other hind limb. He also measured the rate of blood flow through the cannulas. He found that both the blood pressure and the rate of blood flow were greater on the sympathectomized side. He intimates that he did similar or related experiments in 106 other dogs, and that similar results were obtained in them; no details are given. Such evidence strongly supports the contention that, at least in the dog, sympathectomy could dilate collaterals or relieve any spasm of the main or collateral vessels. Since no

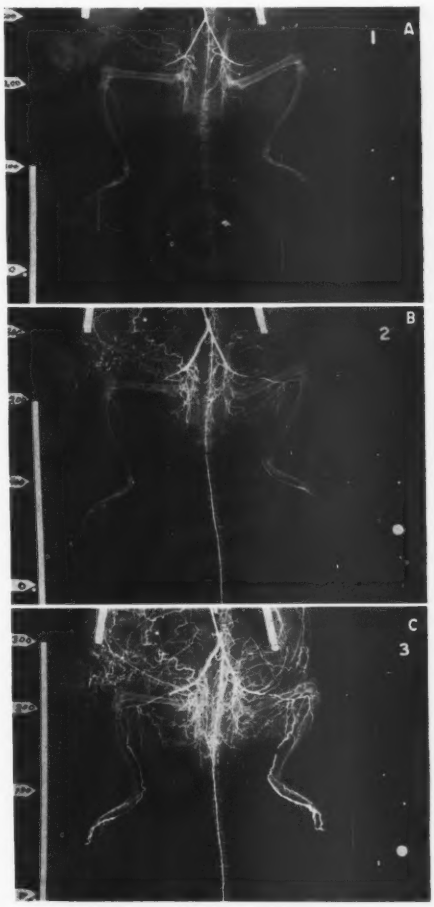

FIG. 1. Mercury angiograms of the hind limbs of a rat, at 100 (*a*), 200 (*b*), and 300 (*c*) mm. Hg as indicated by the mercury column near the right hind limb. The left hind limb artery was ligated one half hour before, and the right immediately before the mercury injection. The collaterals are larger on the ischemic side, since the femoral artery distal to the tie filled at 200 mm. Hg on the left side (*b*) and 300 mm. Hg on the right (*c*).

further work bearing on the question could be found, and since we recently have devised an angiographic method for measuring the size of vessels during life,[19] we attempted to repeat and extend the work of Theis. Preliminary work in the rat showed that after acute arterial occlusion the known changes in the size of collaterals with time could be demonstrated by our angiographic angiometric technic (fig. 1). However, both the rat and rabbit were unsatisfactory animals for this study since it was difficult to be sure one had done a unilateral lumbar sympathectomy that was thorough without having disturbed the sympathetics on the contralateral side. The smallest of the research laboratory animals that sufficed for this purpose was the cat. Since Theis' work was done in the dog, the latter animal was also used, although to a lesser extent, in this work.

Methods

Skin temperature was measured with thermocouples on the ventrum of the paw of the hind limbs, using a Leeds-Northrup potentiometer. Room temperature, body temperature, and forelimb temperatures were also recorded in most experiments. The room temperature was occasionally increased during the experiment, or covers were put over the animal, to help prevent the drop in body temperature (and forelimb and hindlimb temperatures) that tended to occur during and following unilateral lumbar sympathectomy in the cat.

Lumbar sympathectomy was always done on the left side, since it was easier on that side. Four or five ganglia and the intervening chain were removed: one or two ganglia lying above the left renal artery and two or three ganglia lying below the left renal artery. This represented a ganglionectomy from the diaphragm to just below the pelvic brim. The sympathectomy was done either before or after the arterial ligation, just as done by Theis.[18]

The injection of mercury was used to visualize the vessels on the roentgenogram. The injection pressure needed to show filling of the ligated artery distal to the ligature indicated the size of the largest collateral vessel. In previous work[19] we have shown that, given the interfacial tension of mercury against blood, at any given injection pressure the size of the vessel at the place where the front of the mercury comes to rest can be calculated from the formula:

$$d = \frac{11{,}250}{p}$$

where d is the diameter in microns of the vessel at the mercury-blood interface, p is the filling pressure in millimeters of Hg, and 11,250 is the value derived from the known mercury-blood interfacial tension. The data so obtained in regard to the size of the largest arteriovenous communications in various organs appeared to check well with other methods of measurement.[20]

Cats and dogs were utilized and intravenous or intraperitoneal pentobarbital sodium anesthesia was used. We attempted to maintain the animals in light anesthesia throughout the studies. Atropine, given subcutaneously, was also used in some of the cats.

The external iliac or femoral arteries were used. The former were ligated as they arose from the aorta, the latter were ligated below the profunda (below the inguinal ligament). The animals were heparinized before they were injected with the mercury or cannulated for the pressure studies. Various intervals of time were allowed to elapse before proceeding with these studies, so that any effects related to the duration of ischemia might also be noted.

One group of animals was used for the mercury injection study. The abdominal aorta, the renal, superior mesenteric, or the inferior mesenteric artery was cannulated. Use of a branch of the aorta permitted us to leave the circulation to the limbs undisturbed by the mercury injection procedure until just before the actual injection started. At that time the aorta just central to the cannulated portion was ligated and the mercury injection begun. Some of the abdominal vessels were also ligated so as to minimize loss of mercury into these vessels and their collaterals that would only serve to fill the aorta central to the ligature.

Another group of animals was used to study the pressure changes in the artery distal to the tie. Mean blood pressure was measured in the ligated artery about two inches distal to the ligature by cannulation with 18 or 20 gauge needles directed centrally. The artery was tied around the needle. The pressures in the arteries of the two hind limbs were measured alternately and repeatedly, rather than precisely simultaneously, with a mercury manometer. Only one of the animals so studied was also subjected to a mercury study.

Results

Thirty-one cats were used. Skin temperature studies were carried out in 23 of the animals that had bilateral ligation of either the femoral or external iliac arteries and lumbar sympathectomy on the left side only (tables 1, 3, and 4). All exhibited a higher paw temperature on the sympathectomized side except one which showed the same temperature (90 F.) on both hind paws. The temperature differences were greatest in those animals that were not too

deeply anesthetized or not too chilled or shocked by the surgery. Deep anesthesia tended to produce a "chemical sympathectomy" of the unoperated hind limb. A drop in body temperature tended to lower the paw temperature of the sympathectomized limb toward that of the nonsympathectomized limb. The average of the maximum temperature differences obtained in each of the animals was 6.6 F., and the range was 0 to 17.5 F. It is apparent that sympathectomy resulted in an increase of the total blood flow to the skin of the paw.

Satisfactory mercury studies were completed in 12 of 17 animals that had bilateral femoral or external iliac artery ligation and left lumbar sympathectomy. In the other five animals the ties were not placed with exact bilateral symmetry; although the results in these were quite similar to those in the other 12, they have not been included in the reported data. The hind limb arteries were ligated either immediately before the mercury studies (the least time from peripheral arterial ligation to completion of a mercury study was several minutes) or up to 402 minutes before the mercury studies. The sympathectomy was completed 30 to 325 minutes before the mercury studies. The arteries of the two hind limbs were tied approximately simultaneously (within a few minutes of each other). Usually the injection pressure was started at 50 mm. Hg and adjusted upward until the mercury just started to flow into the aorta ("zero" pressure) and then elevated by 30 mm. Hg increments every 30 to 60 seconds, a roentgenogram being taken at each pressure, until mercury was seen in both femoral arteries distal to the ties on direct vision.

In table 1 it can be seen that on the average there was no difference in the size of the largest collateral arterial vessel on the sympathectomized side as compared with the control side. That is, the pressure at which the portion of the femoral artery distal to the tie was filled (as seen on the roentgenogram) was similar in both hind limbs. The series of films in one of the cats is seen in figure 2 (cat 29).

In table 1 it can be seen that the size of the largest collateral vessel varied markedly from animal to animal, and to a lesser degree from one hind limb to the contralateral limb, even when one takes into account the differences in "zero" pressures. It was already noted that the "zero" pressure is that pressure at which the injected mercury just started to flow. Since the cannulas used and the vessels cannulated were large in size, the pressure resisting the inflow of mercury was primarily the blood pressure in the cannulated abdominal vessel after it was tied off centrally (owing to its own collateral circulation).

TABLE 1.—*The Injection Pressure (mm. Hg) at Which the Hind Limb Artery (Distal to the Ligature) Filled in Cats with Bilateral Ligature and Left Lumbar Sympathectomy. Mercury Injection Method.*

Animal	Press. at which Hg flow began in aorta	Press. at which distal lt. hind limb artery filled	Press. at which distal rt. hind limb artery filled	Max. temp. diff. between two hind limb paws (degrees F.)*
W4	90	240	240	2.5
W5	?	380	380	5.5
W11	?	60	60	13.0
W13	?	150	150	13.0
15	50	170	170	5.0
16	110	170	170	5.0
17	70	150	150	5.0
W25	120	200	230	6.0
W26	70	210	140	4.5
W27	50	220	220	2.0
28	90	300	210	10.0
29	90	240	210	0.0

* The temperature was greater on the denervated side in all except cat 29.

It can also be seen that there was no apparent correlation between the differences in paw temperature between the two hind limbs of any one animal and the size of the largest collateral vessel in each of the two limbs. It appeared, then, that the differences in skin temperature between the denervated and innervated limb were not related to the size of the largest collateral present.

As a check on the mercury method under the above experimental circumstances, mercury studies were done in eight cats where one hind limb artery was ligated several hours before the study and the artery of the contralateral limb was ligated only shortly before the study. It is known that some dilatation of the collateral vessels takes place very shortly after

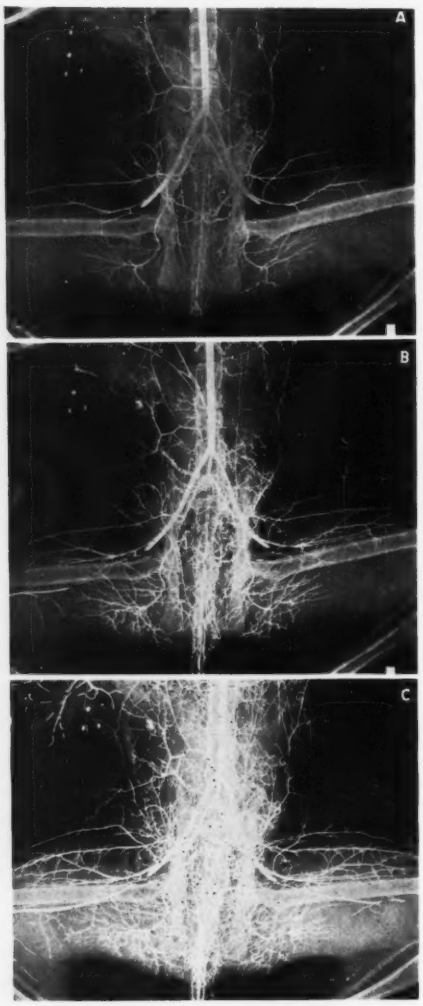

FIG. 2. Mercury angiograms of the hind limbs of a cat, at 90 mm. Hg (*a*), at 120 mm. Hg (*b*), and at 150 mm. Hg (*c*) over the "zero" injection pressure. Bilateral arterial ligation and left lumbar sympathectomy. (*a*) There is no filling of the femoral artery distal to the ligature on either side. (*b*) There is filling on the right side. (*c*) There is also filling on the left side.

ligation of the parent artery, and then there is not much further increase in collateral blood flow until a variable number of hours later.[5, 16, 21, 22, 23] In table 2 it can be seen that the largest collateral vessel frequently had a

TABLE 2.—*The Injection Pressure (mm. Hg) at Which the Hind Limb Artery (Distal to Ligature) Filled in Cats Where One Hind Limb Artery Was Tied Several Hours Before and the Other Just Before the Mercury Injection Study.*

Animal	Lt. hind limb		Rt. hind limb		Press. at which Hg flow began
	Press.	Length of ischemia	Press.	Length of ischemia	
W8	330	5 hrs., 13 min.	330	Several min.	90
23	330	Several min.	240	6 hrs.	70
31	160	Several min.	130	5 hrs., 20 min.	45
32	250	Several min.	130	6 hrs., 15 min.	50
33	320	Several min.	200	6 hrs., 40 min.	40
36	280	Several min.	130	6 hrs., 27 min.	50
37	370	Several min.	280	7 hrs., 35 min.	40
43	280	5 hrs., 53 min.	130	Several min.	50

greater diameter in the limb in which the main artery was ligated about five to seven hours before the mercury study (six of eight cats). In one the reverse was found, and in one there was no difference. The greatest difference was in cat 36 where the femoral artery distal to the tie filled at 80 mm. Hg pressure on the side tied 6 hours and 27 minutes before the mercury study (right) as compared with 230 mm. Hg on the side tied just before the study (left). Using the formula cited previously, this would indicate that the largest collateral on the right was 141 μ in diameter and on the left was 48 μ. Some of the films from that study are shown in figure 3 (cat 36).

Further experiments in eight cats were conducted. The blood pressure in the femoral artery at some distance peripheral to the tie was determined. The data obtained where both external iliac arteries were ligated simultaneously (approximately) and a left lumbar sympathectomy was performed are presented in table 3 (two animals). There was no notable distal femoral artery blood pressure difference between the two hind limbs. That is, the total collateral cross-sectional flow in the denervated limb was similar to that of the other hind limb. The data obtained in six other cats where one external iliac artery was ligated five to seven hours before the study and where the other external iliac artery was ligated im-

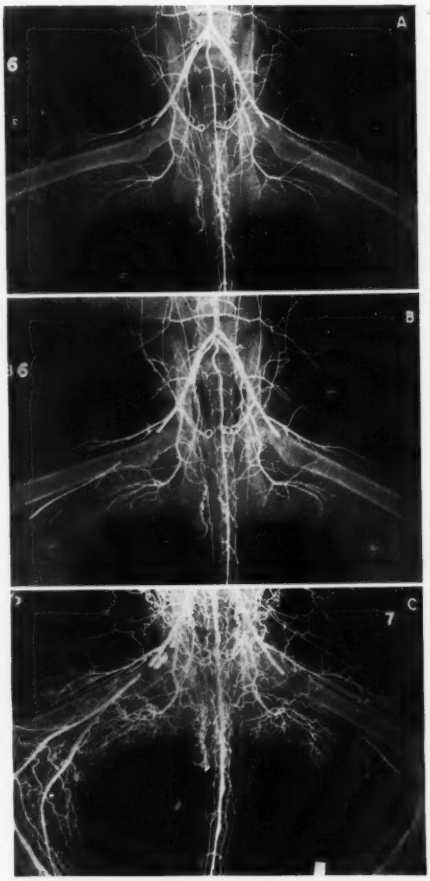

FIG. 3. Mercury angiograms of the hind limbs of a cat, at 50 mm. Hg (*a*), at 80 mm. Hg (*b*), and at 230 mm. Hg (*c*) over the "zero" injection pressure. Arterial ligation on the right was performed just before and on the left 6 hours and 27 minutes before the study. (*a*) There is no filling of the femoral artery distal to the ligature on either side. (*b*) There is filling on the right. (*c*) There is also filling on the left side.

mediately before or during the blood pressure study are presented in table 4. Only one of these animals had a left lumbar sympathectomy (cat 40). It can be seen that the pressure studies were equivocal, probably because of the small number of animals used and the large chance variation in the size and/or number of the collaterals between the two limbs. This variability is also apparent when comparing the preligation femoral artery pressure with the postligation pressure (distal to the tie), as in the first four animals in table 4.

TABLE 3.—*The Mean Blood Pressure (mm. Hg)* in the Hind Limb Artery (Distal to Ligature) of Cats with Bilateral Arterial Ligature and Left Lumbar Sympathectomy.*

Animal	Lt. hind limb	Rt. hind limb	Max. temp. diff. between two hind limb paws (degrees F.)†
21	65–74	58–72	7.5
22	66.5–71	70.5–64	7.0

* These pressures and those in table 4 represent the range of pressures over intervals of time up to 1 hour, but not including the pressures noted during the first several minutes after cannulation.

† The temperature was greater on the denervated side.

In one of the above six cats (cat 43), mercury studies were done following the blood pressure studies (the femoral arteries had to be ligated above and below the site of cannulation). The mercury studies indicated that the largest collateral was significantly larger on the right side. The femoral artery distal to the external iliac ties filled at 130 mm. Hg on the right and 280 mm. Hg on the left side. This corroborates the differences in distal femoral blood pressure noted in this animal in table 4.

Studies similar to those above in the cat were also carried out in the dog. Fourteen dogs were used. They all had a left lumbar sympathectomy. The external iliac arteries or the femoral arteries (distal to the profunda) were tied approximately simultaneously in the two hind limbs, either before or after the sympathectomy. Ten dogs were used for mercury studies and four were used for blood pressure studies (distal to the arterial tie). These studies were done soon after the arteries were tied or within 2 hours and 55 minutes of that time.

The temperature differences between the skin of the sympathectomized hind paws and the innervated hind paws in the 14 dogs varied from 3 to 11.5 F., with an average of 9.1 F. (tables 5 and 6). The size of the largest collateral after bilateral iliac artery ligation and left lumbar sympathectomy was not significantly different on the two sides as measured

TABLE 4.—*The Mean Blood Pressure (mm. Hg) in the Hind Limb Artery of Cats Where One Hind Limb Artery Was Tied Several Hours before and the Other Just before the Study*

Animal	Distal to ligature in lt. hind limb artery		Distal to ligature in rt. hind limb artery		Before ligature was placed in lt. hind artery	Max. temp. diff. between the rt. & lt. hind limbpaws (degrees F.)
	Mean blood press.	Length of ischemia	Mean blood press.	Length of ischemia		
38*	55–88	Several min.	87–106	7 hrs., 2 min.	156	—
39	65	Several min.	66	5 hrs., 48 min.	115	—
40*	58–59	Several min.	62–66	6 hrs., 35 min.	185	17.5 L > R
41	85–90	Several min.	70–72	6 hrs., 40 min.	160	12.0 L > R
42	58–67	5 hrs., 54 min.	51–58	Several min.	—	16.0 R > L
43	67–78	5 hrs., 53 min.	86–98	Several min.	—	—

* Left lumbar sympathectomy was also performed in these two cats.

TABLE 5.—*The Injection Pressure (mm. Hg) at Which the Hind Limb Artery (Distal to Ligature) Filled in Dogs with Bilateral Ligature and Left Lumbar Sympathectomy. Mercury Injection Method.*

Animal	Press. at which Hg flow began in aorta	Press. at which distal lt. hind limb artery filled	Press. at which distal rt. hind limb artery filled	Max. temp. diff. between two hind limb paws (degrees F.)*
A1	?	330	300	11.5
A2	170	210	210	8.0
A4	0	200	200	8.0
A5	?	70	100	10.0
A6	?	140	140	10.0
7	110	170	140	6.5
8	60	130	130	9.0
9	70	120	120	9.5
12	80	140	200	3.0
13	80–150	210	210	11.5

* The temperature was greater on the denervated side in all.

TABLE 6.—*The Mean Blood Pressure* (mm. Hg) in the Hind Limb Artery (Distal to Ligature) of Dogs with Bilateral Arterial Ligature and Left Lumbar Sympathectomy.*

Animal	Lt. hind limb	Rt. hind limb	Max. temp. diff. between two hind limb paws (degrees F.)†
10	45	39	9.0
11	55–64	38–46	9.0
14	18–47	18–36	11.0
15	45–60–48	62–73–52	11.0

* These pressures represent the range of pressures over intervals of time up to but not including the pressures noted during the first several minutes after cannulation.

† The temperature was greater on the denervated side.

by the mercury technic in 10 dogs (table 5). The blood pressure in the femoral artery distal to the ligature in four dogs similarly prepared was greater on the denervated side in three and greater on the control side in one (table 6).

One can see that there was no apparent correlation between size of the largest collateral vessel present or the total collateral cross-sectional flow (arterial blood pressure distal to the tie) and the skin temperature of the paw (tables 5 and 6).

DISCUSSION

The fact that sympathectomy can increase total blood flow to the skin of the toes, as measured by skin temperature, after acute arterial occlusion has been verified in the cat. It could not be shown that this effect was due in any significant degree to an enhancement of the collateral blood flow, as indicated by the size of the largest collateral vessel present (mercury technic) or the aggregate flow in all of the involved collaterals (the blood pressure in the femoral artery distal to the ligature). In the cat, there was no apparent correlation between the differences in skin temperature of the denervated paw as compared with the control paw and the size of the largest collateral present.

Similar findings were recorded in the dog. Sympathectomy resulted in an increase in total blood flow (arteriovenous shunt flow and nutritional flow) to the skin of the paw after acute arterial occlusion. The mercury studies

and the studies of the blood pressure in the femoral artery distal to the ligature indicated that sympathetic denervation did not affect the size of the largest collateral vessel present or the blood pressure.

If an increase in total blood flow in the feet or hands is thought desirable, warming the body may be simpler than, and as effective as, sympathetic block. Without such a study it might be well to attempt to control one's clinical observations by using sympathetic block only after other less contested therapy has not produced a good result within the first one to two hours in patients seen soon after acute arterial occlusion.[5]

One might argue that even if sympathectomy did not dilate normal collaterals it might well dilate those collaterals that might be in spasm in association with the acute arterial occlusion due to embolus or ligature in man.[1, 24] If spasm was present following arterial ligation in the cats and dogs used in our experiments, sympathectomy had no effect on it. Spasm is generally not considered a part of the picture of acute arterial occlusion due to thrombosis, so at least in the latter type of occlusion one might ask for better controls in judging the claimed benefit from sympathetic block. It should probably be stressed that although our studies were conducted under Nembutal anesthesia, the depth of anesthesia was usually not so great as to sympathectomize "chemically" the innervated hind limb, as was indicated by the difference in temperature between the two hind paws.

This work bears no evidence on the possible chronic effects of sympathectomy on the collateral vessels. It is conceivable that in days or weeks sympathectomy might increase the dilatation or the possible new formation of the collaterals. Again however, we would have to show that sympathectomy produced an increase in collateral flow greater than that which apparently occurs with time alone. We have shown in the above experiments that in a relatively short time the collaterals dilate spontaneously. It has also been shown that collaterals continue to dilate spontaneously for longer periods of time.[21, 22, 23, 25]

Conclusions

Sympathectomy can prevent or erase the drop in temperature of the skin of the hind paws of the cat or dog that occurs when the main limb artery is suddenly ligated. By means of an angiographic angiometric technic it was shown that the size of the largest collateral vessel present on the sympathectomized side is the same as that present on the innervated side. Also, by means of blood pressure measurements in the ligated artery distal to the ligature it was shown that sympathectomy produced no increase in collateral blood flow. Therefore, the temperature effects of sympathectomy in acute arterial ligations in the cat and dog is probably due to a shift of blood to the arteriovenous shunts of the toes, in the face of an unchanged flow distal to the arterial ligation.

Since reflex heat and sympathectomy have been claimed to produce similar increases in total blood flow in the skin of the toes of man under most conditions, one might wonder whether reflex heat might not be used in place of sympathetic block in the treatment of acute arterial occlusion in man, if such therapy is thought to be indicated.

Controlled clinical studies are urgently needed on the effect of sympathetic block (or sympathectomy) on the state of tissue ischemia (especially as indicated by sensation and motion in the acral parts) in acute arterial occlusion, when routine therapy including heparinization and reflex heat are already in use.

Sumario Español

El efecto de la simpatectomía en el calibre de los vasos colaterales en la ligación arterial aguda en la extremidad trasera se midió por medio de técnica angiográfica y angiométrica y por determinación de la presión en la parte distal de la arteria ligada. El tamaño del vaso colateral mayor presente en el lado simpatectomizado fué igual al lado inervado. La presión arterial en la parte distal de la arteria ligada fué similar en el lado simpatectomizado y el lado inervado. El aumento usual en temperatura en el lado simpatectomizado fué observado. Esto se puede deber al desvío de sangre de los tejidos profundos de la extremidad

trasera a los "shunts" arteriovenosos de la piel de los dedos, más que a un aumento en la circulación colateral.

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Fluid and Electrolyte Balance during Recovery from High-Output Heart Failure Due to Beri-beri

By Lloyd T. Iseri, M.D., H. S. M. Uhl, M.D., Douglas E. Chandler, M.D., Albert J. Boyle, M.D., and Gordon B. Myers, M.D.

The pathogenesis of congestive heart failure is still obscure. Previous studies showed a decrease in cellular osmolarity during recovery from low output failure. A similar trend was found during recovery from high output failure due to beriberi, suggesting an analogous cellular disturbance. It is postulated that increased cellular osmolarity is an important factor in the retention of water and sodium associated with the development of congestive failure.

STUDIES of water and electrolyte balance during recovery from the usual type of low cardiac output congestive failure have shown cellular uptake of potassium[1-4] and sodium[2, 4] and loss of water.[2, 3] By inference, the development of congestive failure is characterized by changes in the opposite direction, namely, cellular loss of potassium and sodium and gain of water. Such movements of water and electrolytes were explained by the hypothesis that cellular osmolarity increased during circulatory insufficiency.[2, 3] Partial support of this hypothesis was derived from the demonstration of concomitant increase in extracellular osmolarity, as reflected by elevation of plasma sodium concentration in decompensated cardiac patients.[5] The following studies were conducted to investigate the movements of electrolytes and water during recovery from high-output type of congestive heart failure.

Method

Three patients admitted with severe congestive heart failure due to beriberi were studied on the metabolic ward. Cardiac catheterization* was performed soon after admission and before institution of any specific therapy. The cardiac output and the customary intravascular and intracardiac pressures were obtained in each of the three patients. These studies were repeated after recovery from the congestive failure. Specific renal function tests were performed before and after recovery from congestive failure in two of the patients. The renal vein was catheterized and the true renal plasma flow was calculated from para-aminohippurate extraction and clearance. Glomerular filtration rate was obtained by mannitol clearance.

Total balance studies for water, sodium, potassium and chloride were carried out for 8 to 12 days during recovery in each of the three cases. In addition, nitrogen balance was determined in two of the three cases. Metabolic studies were divided into periods of three to five days each and the stools were pooled and analyzed for each period. Urine was collected and analyzed daily. Blood samples were obtained at the beginning of each period and at the conclusion of the metabolic studies. The exact weight of food ingested was determined by weighing all food served and rejected. Foods were prepared by high pressure steam. The electrolyte and nitrogen content of each food was obtained from appropriate tables.[6, 7] The patients were weighed on the Troemmer beam balance.

Intracellular and extracellular partition of water and electrolytes was calculated according to the method of Darrow[8] and Elkinton, Winkler and Danowski.[9] Reference point for the total extracellular volume was selected at the end of the study after edema had been eliminated, 16 per cent of the body weight being taken as equivalent to the extracellular water at that moment.[10] Calculations of the extracellular water were then carried back to the initial period, utilizing the total chloride balance and the plasma chloride concentrations. Primary interest was not in the absolute volume of extracellular water, but, rather, in the changes occurring in this volume during recovery. Changes in extra-

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* Cardiac catheterization studies were performed by Dr. Harper K. Hellems and will be reported in detail in a separate communication.

cellular electrolyte content were then computed from the extracellular volumes and the plasma electrolyte concentrations at the beginning and end of each period. Total body water balance was calculated from changes in weight corrected for true internal nitrogen balance, 1 Gm. of metabolized protein nitrogen being considered equivalent to 33.3 Gm. of tissue weight.[11] Since nitrogen balance was not determined in case 3, no such correction was made. The difference between total and extracellular balance represented intracellular balances. The insensible loss of weight was determined according to the method of Newburg.[12] This was assumed to be essentially equal to insensible loss of water. The total intracellular osmolar change was calculated by Elkinton's method.[3]

Sodium and potassium were analyzed by flame-photometry, according to methods described previously.[13] Chloride was determined manometrically[14] and polarographically,[15] and nitrogen was determined by micro-Kjeldahl method.[16]

Case Reports

Case 1 (D. R. H. no. 50-15252)

L. P., a 53 year old male bartender, was admitted on Nov. 1, 1950 because of severe dyspnea and edema. There was a weight gain of 35 pounds over the preceding two months, and for 10 days prior to admission there was progressive swelling of ankles, legs and abdomen, followed by dyspnea and orthopnea. There was a slight nonproductive cough. Review of the past history revealed no evidence suggestive of cardiovascular, pulmonary, or renal diseases. There was, however, a long history of chronic alcoholism and poor dietary intake.

Physical Examination. The patient was a well-developed, plethoric white male with anasarca and orthopnea. The blood pressure was 130/60. No evidence of hypertension was seen in the ocular fundi. A conspicuous rhinophyma and dilated telangiectasiae of the cheeks were present. The skin was flushed and warm. The tongue was smooth, red and atrophic. Neck veins were distended. There was a pleural effusion on the right and moist rales were heard above this and in the left base. The heart was enlarged to both right and left. A diffuse apical impulse with a rate of 140 per minute was felt. There was a mesodiastolic gallop and a soft systolic murmur at the apex. The abdomen was protuberant with ascites and edema of the wall. A tender liver extended 6 cm. below the right costal margin. The genitalia and extremities showed massive edema and the skin over the legs was indurated and brawny. Neurologic examination revealed no abnormalities.

Laboratory Studies. The complete blood count was normal except for hemoglobin of 10 Gm. per 100 cc. The hematocrit was 40 per cent. Urinalysis was negative except for 1 plus albuminuria. Fasting blood sugar was 92 mg. per 100 cc.; nonprotein nitrogen, 70 mg. per 100 cc.; serum albumin, 4.99 Gm.; serum globulin, 2.06 Gm.; and serum bilirubin, 2.4 mg. per 100 cc. The Kline test was negative. Plasma sodium concentration was 129 mEq.; potassium, 5 3 mEq.; chloride, 101.1 mEq. per liter; and carbon dioxide combining power, 32 volumes per cent. Chest x-ray films and fluoroscopy showed congestion of the lungs, right pleural effusion, and a poorly contracting, hyperactive heart, which was enlarged to 60.5 per cent of the diameter of the chest. The electrocardiogram showed sinus tachycardia and low voltage complexes in all leads. The basal metabolic rate was plus 35 per cent. The arm-to-tongue circulation time, using Decholin, was 17 seconds, and the venous pressure was 340 mm. of water. Total plasma volume, using T-1824 dye, was 6,894 ml. and the total blood volume, 11,423 ml. Soon after admission 1300 ml. of straw-colored pleural effusion were removed.

Hospital Course. Cardiac catheterization studies, performed on the third day, demonstrated an increase in right ventricular diastolic and pulmonary "capillary" pressures. The cardiac output was 14.4 liters per minute and the cardiac index, based on "dry weight," was 7.75 liters. The arteriovenous oxygen difference and the peripheral vascular resistance were well below normal. These findings were consistent with high-output failure due to beriberi.[17, 18]

The first two hospital days constituted a brief control period on bed rest and a 200 mg. sodium diet without supplementary vitamins. Dyspnea was partially relieved initially by thoracentesis. There was an additional weight loss of 2.5 Kg. over the 48-hour period. No change in physical findings with respect to heart and peripheral vessels was observed.

Following cardiac catheterization on the third day of metabolic study, the patient was started on 200 mg. of crystalline thiamine hydrochloride, intramuscularly, three times a day, and, in addition, was given supplementary oral "B" complex vitamins. He was also kept on a weighed 200 mg. sodium diet. On this regimen, the patient improved rapidly and steadily with disappearance of peripheral and pulmonary congestion and with a decrease in cardiothoracic ratio to 48.5 per cent. The venous pressure fell to 90 mm. of water and the circulation time fell to 12 seconds. The plasma volume on the ninth day was 6,250 ml. The metabolic studies were continued from the first through the twelfth day, by which time the edema had all disappeared and the weight had stabilized at approximately 34 Kg. below the initial weight.

Cardiac catheterization, performed again after full compensation of cardiovascular function, showed a decrease in cardiac index to 5.8 liters per minute, a decrease in end-diastolic right ventricular and pulmonary "capillary" pressures to normal,

and an increase in arteriovenous oxygen difference and peripheral vascular resistance.

Case 2 (D. R. H. no. 51-4151)

L. B., a 40 year old white male, brewery employee, was admitted on March 20, 1951 because of severe swelling of the lower extremities, genitalia and abdomen. The patient was a chronic alcoholic and had been drinking excessively for five months, averaging 40 to 50 bottles of beer per day. His intake of food became progressively more restricted and, with the development of anorexia in the few weeks preceding his admission, was virtually nil. For one week before admission, he noted increasing dyspnea and progressive edema, but denied orthopnea, palpitation and cough. For two days he suffered from pain in his calves, but gave no other symptoms of peripheral neuritis. A careful interrogation of his past medical history revealed no evidence of any previous cardiovascular, pulmonary or renal disease.

Physical Examination. The patient was a well-developed white male with warm flushed skin and anasarca. The temperature, pulse, and respirations were normal and the blood pressure was 115/65. The sclerae were slightly icteric. The fundi showed no evidence of hypertension. The tongue was smooth and red, and perlèche was present. There was no thyroid enlargement or evidence of hyperthyroidism. Occasional rales were heard in both lower lobes and signs of pleural effusion were present in the left. The heart was enlarged and a protodiastolic gallop and a soft systolic murmur were heard at the apex. The abdomen was protuberant and signs of ascites were present. A tender liver was palpable 10 cm. below the right costal margin. The spleen and kidneys could not be felt. The external genitalia and the lower extremities revealed marked pitting edema. Neurologic examination revealed bilateral calf tenderness, plantar hyperalgesia, and decreased knee and ankle jerks.

Laboratory Studies. The hemoglobin was 12.0 Gm. per 100 cc. and the hematocrit, 42 per cent. Urinalysis was negative. Serologic tests for syphilis were negative. Blood urea nitrogen was 9 mg. per 100 cc.; total serum protein, 5.97 Gm. per 100 cc. with 3.65 Gm. albumin and 2.32 Gm. globulin per 100 cc. Total serum bilirubin was 1.2 mg. per 100 cc., and inorganic phosphorus 6.5 mg. per 100 cc. Plasma carbon dioxide combining power was 35 volumes per cent; sodium, 136, and potassium 3.6 mEq. per liter. The cephalin flocculation test was 1 plus in 24 hours. Total plasma volume was 4,310 ml., and the total blood volume was 7,431 ml. The electrocardiogram was suggestive of right ventricular dilatation. Arm-to-tongue circulation time was 11 seconds, and the venous pressure 168 mm. of water. Chest x-ray films showed a cardiothoracic ratio of 51.2 per cent, pulmonary congestion, and mild emphysema.

Hospital Course. Cardiac and renal vein catheterization was performed on the second and twenty-first days of hospitalization. The initial studies, which required 450 ml. of saline during the procedure, showed a cardiac output of 8.33 liters per minute and a "dry weight" cardiac index of 4.73 liters per minute. End-diastolic right ventricular and pulmonary "capillary" pressures were elevated, whereas the arteriovenous oxygen difference and the peripheral vascular resistance were decreased. In spite of the high cardiac output, the true renal blood flow was decreased, so that the fraction of cardiac output going to the kidneys was only 5.8 per cent. There was proportionately less reduction in glomerular filtration rate than in renal plasma flow, with consequent elevation in filtration fraction to 35.0 per cent. Following the initial studies and during the 10-day metabolic period, the patient was maintained on a weighed 200 mg. sodium diet rich in vitamins. No cardiac glycosides, diuretics or supplementary vitamins were given. The plasma volume and blood volume fell to 2,873 and 5,861 ml., respectively. The patient lost over 16 Kg. of fluid and showed improvement in both cardiac and renal functions. Pulmonary rales and signs of pleural fluid and peripheral edema disappeared. The cardiothoracic ratio decreased from 51.2 to 43.6 per cent. Venous pressure fell to 85 mm. of water, but the circulation time lengthened slightly to 14 seconds. The end-diastolic right ventricular and pulmonary "capillary" pressures fell to normal levels. There was, however, a paradoxic increase in cardiac output to 11.15 liters per minute, directly referable to considerable amount of apprehension, obvious during the second cardiac catheterization procedure. Both renal plasma flow and glomerular filtration rate became normal, as did the filtration fraction and the renal blood flow–cardiac output ratio.

The metabolic studies in this patient were carried out for 10 days from the second to eleventh day, inclusively, in two five-day periods.

Case 3 (D. R. H. no. 51-15894)

J. K., a 34 year old white male laborer, was admitted on Nov. 19, 1951 because of severe progressive dyspnea. There was a long history of chronic alcoholism, poor diet, and neglected personal hygiene. Exertional dyspnea had been noted intermittently for five years. This had become increasingly severe during the last year and was complicated by dependent edema over the last five months and swelling of the abdomen for one month. A chronic cough had been productive of a white frothy sputum, but hemoptysis had never occurred. On the day of admission, there was an exacerbation of cough and dyspnea, accompanied by fever, but not by chills or pleural pain. Past history was otherwise negative.

Physical Examination. The patient was an obese, orthopneic white male. The temperature was 101 F., pulse 100 per minute, and respirations 24 per minute. The blood pressure was 140/75. The skin was warm and flushed. The fundi showed no evidence of ante-

cedent hypertension. Signs of avitaminosis were evident in the tongue. The neck veins were distended. The trachea was in the midline and the thyroid was not palpable. A slight enlargement of the heart was present, with the apical impulse beyond the midclavicular line The heart was hyperactive, with a regular rhythm and a rate of 104 per minute. The heart sounds were of poor quality and a soft systolic murmur was heard at the apex. The lungs revealed scattered rhonchi, fine rales at the bases, and definite signs of early pneumonic consolidation of the right upper lobe. The abdomen was distended with ascites. The liver was enlarged 5 fingerbreadths below the right costal margin and was firm, but nontender and nonpulsatile. The spleen could not be felt. There was marked tenderness of the calves, but there were no associated signs of peripheral neuritis. There was moderate soft pitting edema of the lower extremities and the trunk.

Laboratory Studies. A complete blood count showed a hemoglobin of 13.0 Gm. per 100 cc., hematocrit of 50.2 per cent, white blood cells 13,600 per cu. mm., with 84 per cent polymorphonuclears, 6 per cent lymphocytes, and 8 per cent monocytes. The Westergren sedimentation rate was 18 mm. in one hour. Urinalysis was negative. The sputum contained type III pneumococci. On admission, the blood urea nitrogen was 12 mg. per cent, plasma carbon dioxide combining power 50 volumes per cent, plasma chloride 96 mEq. per liter, plasma sodium 140 mEq. per liter, and plasma potassium 5.9 mEq. per liter. The total serum bilirubin on the seventh day was 1.2 mg. per 100 cc. Total serum protein was 7.6 Gm. per 100 cc., with 3.9 Gm. of albumin and 3.7 Gm. of globulin. Liver function studies showed a prothrombin time 85 per cent of normal, cephalin flocculation 3 plus in 24 hours, and bromsulphalein retention of 26 per cent in 45 minutes. Roentgenogram of the chest on admission showed a slightly enlarged heart, 49.5 per cent of intrathoracic diameter, and a pneumonitis of the right upper lung field. There was no pleural effusion. The arm-to-tongue circulation time, using Decholin, was 9 seconds, and the venous pressure was 150 mm. of water.

Hospital Course. Intensive antibiotic therapy was instituted and effected considerable improvement in the pneumonia, reducing the temperature to 99 F. on the second hospital day, when cardiac catheterization and renal function studies were performed. The cardiovascular-pulmonary hemodynamic measurements confirmed the clinical impression of high-output heart disease with left and right ventricular failure. The cardiac output was 11.4 liters per minute and the cardiac index 5.8 liters per minute The peripheral vascular resistance was markedly decreased, but the arteriovenous oxygen difference was within normal limits. It is noteworthy that the renal plasma flow and the renal blood flow were normal. The glomerular filtration rate was supernormal.

Following this initial evaluation of cardiac and renal function, the patient received thiamine, 100 mg. three times a day, with other vitamins of the "B" complex group.

Digitalis and mercurial diuretics were withheld. Sodium intake was limited to 200 mg. daily.

On this regimen the heart became compensated. There was a weight loss of 4.8 Kg. during the first two days before metabolic studies were instituted and a total loss of 10.4 Kg. over the first 10 days with complete disappearance of the peripheral edema. A decrease of cardiothoracic ratio to 42.2 per cent was evident on the x-ray films. The venous pressure and circulation time showed only minimal changes. Cardiac and renal vein catheterizations were repeated four weeks after admission. The cardiac output, pulmonary capillary pressure and right ventricular pressure decreased to normal, and the peripheral vascular resistance increased to a nearly normal value. There was no change in the true renal plasma flow, but the glomerular filtration rate fell from supernormal to normal values.

The metabolic studies were carried out for eight days, from the third to the tenth day, inclusive. The study was divided into two four-day periods.

Results of the Metabolic Studies

The results of the metabolic studies carried out during recovery in each of the three patients proven to have a high-output type of congestive heart failure are presented in tables 1 and 2.

Changes in Water Metabolism. As expected, all three patients lost weight during the 8- to 12-day period of study. The total water balance, estimated from weight changes and corrected for true nitrogen balance in cases 1 and 2, but not corrected in case 3, indicated a total loss of 22.02, 17.71 and 5.50 Kg. water, respectively.

Calculation of extracellular water balance demonstrated total losses of 20.70, 19.52, and 2.25 Kg. in each of the three cases, respectively. Loss of extracellular water was maximal during the first period in cases 2 and 3 and appeared to represent a prompt response to either dietary or supplementary thiamine. In case 1, the greater loss of extracellular water occurred during period II, presumably due to delay in specific therapy. The total extracellular water at the onset of study was calculated to be 34, 41, and 17.6 per cent of the edematous body weight, respectively, in the three cases.

TABLE 1.—*Intake and Output Data*

Patient	Period Days	Weight Kg.	Intake					Output										Plasma			Blood
								Urine					Stool								
			H_2O ml.	Na mEq.	K mEq.	Cl mEq.	N Gm.	Vol. ml.	Na mEq.	K mEq.	Cl mEq.	N Gm.	Wt. Gm.	Na mEq.	K mEq.	Cl mEq.	N Gm.	Na mEq./L.	K mEq./L.	Cl mEq./L.	NPN mg./100 ml.
Case 1	I	94.27	9,207	51	365	135	52.0	11,050	233	425	398	87.6	440§	8	27	5	1.3	129	5.3	101.1	70
L. P.	1–4																				
	II	87.03	10,575	26	386	113	51.1	14,950	1258	258	1002	81.6	440§	8	27	5	1.3	146	3.8	102.3	32
	5–8																				
	III	77.70	8,993	36	589	325	44.8	15,625	1221	535	1039	72.7	111	1	17	2	0.4	144	4.5	111.0	34
	9–12	69.99*																150*	4.8*	119.5*	42*
Case 2	I	80.53	20,910	110	463	199	58.8	26,125	1362	283	1479	33.8	717	21	73	136	3.6	136	3.6	100.5	28
L. B.	2–6																				
	II	67.80	17,954	51	540	155	70.6	19,600	495	385	664	47.1	350	23	35	6	2.0	136	4.8	94.4	31
	7–11	64.40*																149*	4.1*	103.5*	33*
Case 3	I	92.7	18,555	41	401	116	—	13,450	549	272	391	—	1428	13	36	11	—	140	3.8	105.8	14‡
J. K.	3–6																				
	II	90.0	18,238	42	515	137	—	13,100	93	308	161	—	1657	20	54	8	—	136	4.7	103.7	12
	7–10	87.2*																133†	4.5*	99.7†	11*

* Values obtained at end of study. Other values obtained at beginning of each period. † Interpolated between preceding values and values obtained four days later. ‡ Blood urea nitrogen. § One-half of eight-day pooled sample.

TABLE 2.—*Derived Values of Total, Extracellular, and Intracellular Balances*

Patient	Period Days	Total Balance					Extracellular Balance			Intracellular Balance			Extracellular Volume L.	Insens. Loss of Weight ml./d.	Total Intracellular Osmolar Change ¶ mEq.
		H_2O* Kg.	Na mEq.	K mEq.	Cl mEq.	N† Gm.	H_2O Kg.	Na mEq.	K mEq.	H_2O Kg.	Na mEq.	K† mEq.			
Case 1	I														
L. P.	1–4	−6.95	−190	−87	−268	−8.7	−3.15	+72	−60	−3.80	−262	−6	31.90	2,045	+283.8
	II														
	5–8	−8.33	−1240	+101	−894	−29.9	−10.19	−1532	−26	+1.86	+292	+199	28.75	1,968	−332.8
	III												18.50		
	9–12	−6.74	−1186	+37	−716	−29.1	−7.36	−981	−30	+0.62	−205	+136	11.20§	1,240	+301.3
Case 2	I														
L. B.	2–6	−13.52	−1273	+106	−1416	+23.6	−13.07	−1778	−27	−0.45	+505	+76	29.82	2,177	−750.7
	II												16.75		
	7–11	−4.19	−467	+120	−515	+21.8	−6.45	−746	−39	+2.26	+279	+106	10.30§	1,426	+306.2
Case 3	I														
J. K.	3–6	−2.70	−521	+93	−286	—	−2.40	−391	+3	−0.30	−130	+90	16.20	2,540	−204.6
	II												13.80		
	7–10	−2.80	−71	+153	−32	—	+0.15	−21	−2	−2.95	−50	+155	13.95§	2,865	−652.8

* Change in weight corrected for true nitrogen balance (1 Gm. N = 3.33 Gm. H_2O).

† True internal nitrogen balance (corrected for total nonprotein nitrogen balance calculated on assumption of equal distribution of nonprotein nitrogen throughout entire body fluids).

‡ Corrected for true nitrogen balance (1 Gm. N = 2.4 mEq. K) in cases 1 and 2.

§ Final extracellular volume (16% of compensated weight).

¶ Corrected for true nitrogen balance in cases 1 and 2.

The extracellular volume shrank progressively throughout the first 10 days of study in cases 1 and 2 and reached a minimum by the end of five days in case 3. The intracellular water balance was negative in cases 1 and 3, but positive in case 2.

There was considerable insensible loss of weight, exceeding 2.0 Kg. per day. during the

initial period of study in all three cases. With recovery, the insensible loss decreased progressively in the first two cases, but remained elevated in the last.

Changes in Sodium Metabolism. The sodium ion was eliminated from the body in large quantities, the total external balance being −2,616, −1,739, and −502 mEq. for the entire period of study, respectively, in the three cases. Naturesis occurred promptly in the first period in cases 2 and 3, but was delayed until the administration of thiamine in case 1, as shown in table 3. The urinary sodium concentration was very low during the two-day control period and rose abruptly and progressively after institution of thiamin to reach a maximum on the sixth day of treatment.

The total intracellular sodium balance over the entire period of study was quite variable, being negative in cases 1 and 3, but markedly positive in case 2. The variability was also apparent during the separate periods of observation in case 1. These variations may have been due, in part, to the possible inherent error in utilizing chloride balance as a criterion of extracellular balance.

Changes in Potassium Metabolism. All three patients had a positive total potassium balance,

TABLE 3.—*Case 1. Effect of Thiamine Therapy on Sodium and Potassium Excretion in Beriberi Heart Disease*

Period	Day	Urine Output *ml.*	Urine Na Conc. *mEq./L.*	Urine K Conc. *mEq./L.*	Plasma Na Conc. *mEq./L.*	Plasma K Conc. *mEq./L.*
I	1	1700	3.0	52.4	129.0	5.3
	2	1800	3.2	46.7		
	3*	3650	21.9	41.2		
	4	3900	36.8	21.7		
II	5	2700	52.8	18.4	146.1	3.8
	6	4125	77.5	13.6		
	7	4100	97.9	15.9		
	8	4025	99.0	21.8		
III	9	4700	89.3	18.5	143.6	4.5
	10	4900	82.8	25.7		
	11	3475	81.3	50.0		
	12	2550	44.8	58.5		
	13				149.9	4.9

* Beginning of thiamine therapy.

resulting from cellular uptake. After correction of extracellular balance and the internal nitrogen balance, the intracellular potassium balance was +329 mEq. in case 1 and +18 mEq. in case 2. The intracellular balance, uncorrected for nitrogen, in case 3 was +25 mEq.

Cellular uptake of potassium in cases 2 and 3 was greater during the last half of the study than during the first half. In case 1 the balance was slightly negative during the initial period but became strongly positive for the remainder of the study. The delay in uptake in case 1 was correlated with the poor renal conservation of potassium, which was present for two days before and on the day of institution of thiamine (table 3).

Total Change in Osmolar Activity of Intracellular Base. This was derived from the difference between the calculated total osmotically active base at the end and beginning of the period, corrected for the measured external balances of sodium and potassium.[3] A negative value implies binding of osmotically active electrolyte in the body fluids into inactive complexes, and a positive value implies the reverse change. Since osmotically inactive base is negligible in the extracellular fluid, the data would represent intracellular changes. It must be admitted, however, that an indeterminate fraction of the changes in osmolar activity may occur in the bones.[19] In cases 2 and 3 the total osmolar change over the entire period of observation was negative, signifying inactivation of cellular base. In case 1, the change during period I was positive, presumably from correction of the initial hyponatremia and delay in therapy. During period II the osmolar change was negative, although much of this was again reversed during period III.

DISCUSSION

In each of the three cases reported in this study, a diagnosis of congestive heart failure of the high-output type, due to beriberi, was made on the basis of the history of chronic alcoholism with poor dietary intake; avitaminosis; absence of pericardial, valvular or the usual myocardial diseases; congestive edema,

with elevated venous, right ventricular diastolic, and pulmonary "capillary" pressures; signs of hyperactive heart with increased pulse pressure and shortened circulation time; high cardiac output by direct measurements; and peripheral vasodilation with flushed warm skin, low arteriovenous oxygen difference, and low peripheral vascular resistances. Although blood lactate and pyruvate levels were not obtained, the improvement of all three patients on dietary and/or supplementary thiamin, without the use of digitalis or mercurial preparations, substantiated the diagnosis.

The metabolic studies during recovery in these three cases revealed a comparable trend to that observed during recovery from low-output failure.[2, 3] There was a pronounced cellular uptake of potassium in all three cases, and a significant negative intracellular water balance in two. The net result in all three cases indicated movements of sodium, potassium, and water in such a manner, which tended to increase the concentration of electrolytes in the cells. The capacity of the cells to take up additional electrolyte during recovery is presumably dependent upon osmotic inactivation of cellular base. This was demonstrable in cases 2 and 3.

Thus, the development of both low- and high-output congestive failure would, by inference, be accompanied by activation of cellular base.[2] Squires, Crosley and Elkinton[3] reached a similar conclusion, and the results obtained by Miller[20] could be interpreted in the same manner. A primary increase in cellular osmolarity may lead to cellular extrusion of electrolytes and uptake of water, and may stimulate the kidneys (1) to retain water, through antidiuretic hormone,[21] in order to lower the cellular osmolarity, and (2) to retain sodium, possibly through corticoid activity,[22] in order to raise the extracellular osmolarity and maintain equilibrium.[5] The characteristic interstitial edema would result when the excess water and sodium, retained during exercise, are incompletely eliminated during the succeeding rest.

In low-output failure, increased cellular osmolarity may be attributed to primary cardiac insufficiency with accumulation of metabolites in the tissues either from incomplete removal or from decreased oxygen transport[23] and impaired oxidation. In beriberi, on the other hand, congestive failure may occur in the presence of high oxygen transport and may develop in the absence of myocardial failure.[24] Moreover, in the present study, edema antedated dyspnea in one case, and occurred in the presence of normal renal blood flow in another. If myocardial failure, decreased renal blood flow and decreased oxygen transport are not obligatory for the development of edema in beriberi, the disturbance in the cells may be the primary factor provoking retention of sodium and water. Increased cellular osmolarity in beriberi may be the result of accumulation of pyruvate and lactate ions in the tissues and may be the initial step in the vicious cycle which eventuates in myocardial failure and reduced renal blood flow.

Summary

In three cases of beriberi with high-output congestive failure, established by clinical criteria together with cardiac catheterization, metabolic balances of sodium, potassium, chloride and water were determined during the period of recovery on a regimen consisting of bed rest, low sodium, and a vitamin-rich diet with or without thiamine supplements. Nitrogen balance was studied in two of the cases. Cellular uptake of potassium with or without sodium and cellular ejection of water was demonstrated in these patients. The consequent osmotic inactivation of cellular base was comparable with that associated with recovery from low-output congestive failure. The findings are discussed from the standpoint of pathogenesis of congestive heart failure.

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Sumario Español

En tres casos de beriberi en decompensación cardíaca de alta producción, establecida

mediante criterio clínico además de cateterismo cardíaco, estudios metabólicos del balancee del sodio, potasio, cloruros y agua se determinaron durante el período de recuperación en un regimen que consistió en descanso en cama, bajo sodio y una dieta rica en vitaminas con y sin suplementos de tiamina. Estudios de balance de nitrógeno fueron hechos en dos casos. El "uptake" celular para el potasio con o sin el sodio y la expulsión de agua se demostró en estos pacientes. La consiguiente inactivación osmótica de base celular fué comparable con aquella asociada al recobro de la decompensación cardíaca de tipo de baja producción. Los hallazgos se discuten desde el punto de vista de la patogénesis de la decompensación cardíaca.

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Electrocardiographic Leads

II. Analysis

By Richard McFee, M.S., and Franklin D. Johnston, M.D.

In this second paper of a series of three on electrocardiographic leads, presented primarily from the standpoint of an electrical engineer or physicist, the concept of the lead field introduced in the first paper is considered in detail and several necessarily indirect methods for the estimation of these fields are presented.

IN the first paper of this series[1] it was shown that the relationship between the electromotive forces of the heart and the voltages produced by them in a given lead are completely determined by the electric field set up in the heart when a unit current is introduced into the lead. This means that to analyze the relationship between the electromotive forces and the lead voltage it is only necessary to determine the nature of the lead field. A brief discussion of various methods of studying these fields is given in this paper.

When a current is introduced into a lead the resultant flow of current through the heart produces potential differences between various points in the muscle. If it were possible to measure these potential differences, this data would furnish the desired information about the field. Unfortunately, it is not possible to do this with human subjects. For this reason it is necessary to resort to other approaches, all essentially indirect.

The simpler of these approaches furnish graphic patterns in which one component of the lead field current is taken as zero. Such two-dimensional patterns are easy to obtain and to interpret, and frequently give an insight into the nature of the lead which would be quite difficult to obtain from three dimensional data, since the latter cannot be conveniently represented graphically. However, unless one component of the actual lead field is small (as is probably the case with the standard leads) the patterns obtained from such studies cannot be used for quantitative purposes, such as estimating the accuracy of a certain interpretation of a lead. To obtain quantitative information, three dimensional studies are usually necessary. These are much more difficult than the two-dimensional ones, not only because of the extra dimension and the greater accuracy usually sought for, but also because of the difficulty in representing the data about the field in a fashion easily grasped.

In this paper both two- and three-dimensional methods for studying the fields are considered, but only the basic principle and the highlights of each method are given. For the convenience of the average reader, nearly all mathematical considerations have been placed in the appendices. Some of the important problems associated with the analysis of leads, such as the "validity" of the Einthoven triangle and Wilson central terminal, are touched upon in the discussion.

Two-Dimensional Approaches

Sketching the Fields. A surprising amount of information about lead fields can be obtained from simple sketches of the flow lines, based upon intuition. The ability to do this naturally improves with practice. It is worth while to keep in mind the analogy between the flow of water (without turbulence or eddies) and the flow of electricity. To the extent that the body is electrically homogeneous, it may be thought of as a hollow container into which water rather than electricity is entering or leaving the body at the lead electrodes. To

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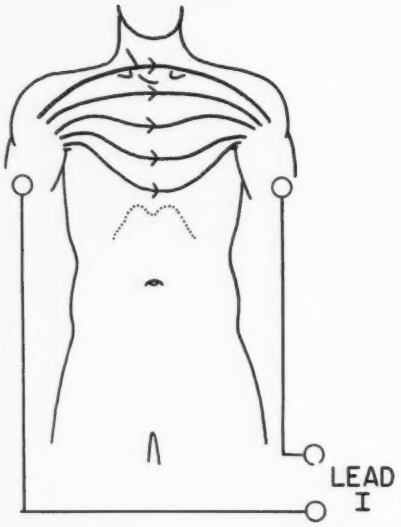

FIG. 1. Sketch of field of lead I

illustrate the idea involved here, consider lead I. If the body were hollow and if water were to enter the body at the right arm and leave from the left, the flow lines would be more or less like those shown in figure 1. From the symmetry of the body it is clear that, if the heart were located in the center of the chest, the direction of the flow lines within it would, on the average, be transverse, in general agreement with Einthoven's interpretation of lead I. However, since the heart is usually located a little to the left of center, the flow lines within it will tend to point slightly upward, and this in turn means that lead I is probably influenced slightly by the vertical component of the heart vector.

It is quite obvious, even from rough sketches of the lead fields involved, that most leads used at present for obtaining the sagittal component of the heart vector are far from satisfactory. For example, consider the lead proposed by Duchosal and Sulzer.[2] A sketch of the field of this lead is shown in figure 2*A*, and should be compared with the field desired, which is sketched in figure 2*B*. The field of the Duchosal's lead suffers most from having the wrong average direction, and it is possible that the lead, as a result, is as sensitive to the

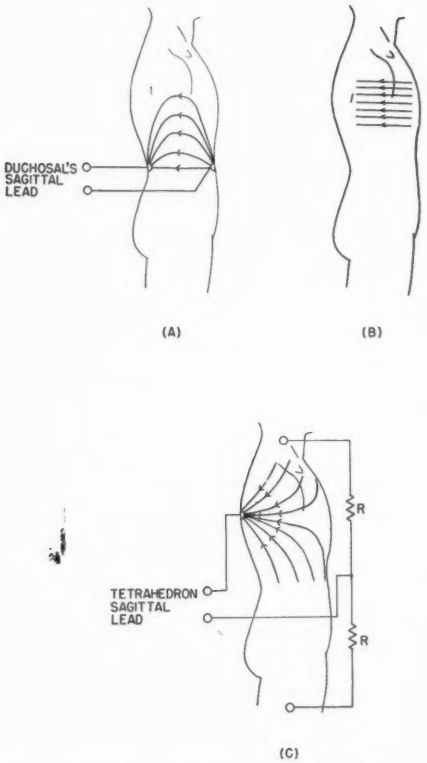

FIG. 2. Sketches of fields of leads for determining sagittal component of heart vector. (*A*) Duchosal and Sulzer's lead, (*B*) perfect lead, (*C*) tetrahedron lead.

vertical component of the heart vector as it is to the sagittal component.*

The field associated with the lead formed by the back electrode of the tetrahedron[3] and a second electrode connected via equal resistances to the foot and neck is sketched in figure 2*C*. (This second electrode is the two-dimensional equivalent of the central terminal.) Although this field has the correct average direction, it is by no means uniform. Evidently the lead is much more sensitive to electromotive forces on the back of the heart than to those in front; that is, the lead acts more like a proximal or chest lead than like a heart vector lead.

* Where the three-dimensional situation is considered, a transverse component is probably involved also.

It is not difficult to see from the ideal sagittal lead pattern shown in figure 2*B* how a sagittal lead must be constructed. This topic will be treated in the next paper, but in the meantime the curious reader may find it interesting and illuminating to try to work out this lead for himself.

Fluid Mappers. The hydraulic analogy mentioned previously in connection with sketches of the field is the basic principle of simple devices for studying the flow patterns, which are called "fluid mappers." Their application to electrocardiographic problems has been described in detail in a recent paper by McFee, Stow and Johnston.[4] In fluid mappers the water flows in sheets between a glass plate and a flat plaster slab, past small crystals of soluble dye, which dissolve slowly, thus making the lines of flow visible. The effective resistance to the flow of water, which corresponds to the electrical resistance of the tissues of the body, is easily varied by changing the depth of the "flow space;" that is, by altering the thickness of the fluid sheet.

Figure 3 shows a typical fluid mapper pattern. It represents the field of a lead formed by an exploring electrode on the precordium and a second electrode representing the central terminal, which is connected to the foot and neck through equal resistances. The depth of the flow space in figure 3*A* is constant, while in figure 3*B* it is so altered that the resistance of the area representing the heart is one-fourth that of the other regions of the mapper. These mappers were built in order to find to what extent the central terminal is "indifferent" when the exploring electrode is over the heart. As was pointed out in the first paper of this series, if the central terminal were "indifferent," the flow lines *within the heart* would appear to radiate from the exploring electrode in straight lines. Inspection of both patterns indicates that this is not far from the case.

Fluid mapper patterns furnish no direct information concerning the intensity of the field at various points. However, this information can be obtained by careful study of the flow lines and isopotential lines in a manner which is described in appendix I.

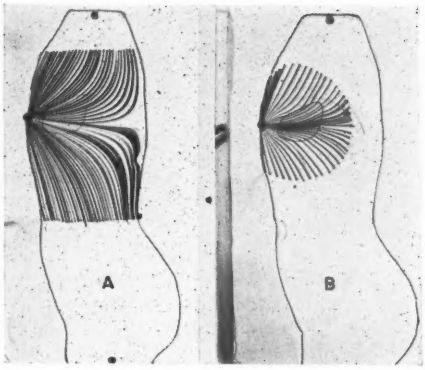

FIG. 3. Fluid mapper patterns of central terminal chest leads. (*A*) Body has uniform conductivity; (*B*) heart has twice conductivity of rest of body.

*Conducting Paper Mannikins.** Two-dimensional lead fields in homogeneous media may be studied in a simple fashion by using conducting paper.† This paper comes coated with a thin even layer of a material having a moderate electrical resistance. The paper is cut to the desired outline, and tacks are applied to the sites of the electrodes of the lead. The electrodes are then connected via resistances (30,000 to 300,000 ohms) to a battery (45 to 450 volts) and the resulting field in the paper established with two needle-tipped probes and a sensitive vacuum tube voltmeter (either 1 or 3 volts, full scale, input resistance around 10 million ohms). The voltage measured will be zero if the two electrodes are on the same isopotential, and this fact enables one to locate quickly many such points. After this has been done the isopotential lines can be drawn with the help of a French curve. Figure 4 shows an isopotential pattern of a special chest lead which has been obtained using this method. This lead, which is called a "null" lead, will be discussed shortly.

Fields on the Chest Surface. It is relatively

* Since the writing of this paper the authors have learned that a similar use of these mannikins has been made by Brody and Romans.[12]

† "Teledeltos" paper. The Western Union Company, New York City.

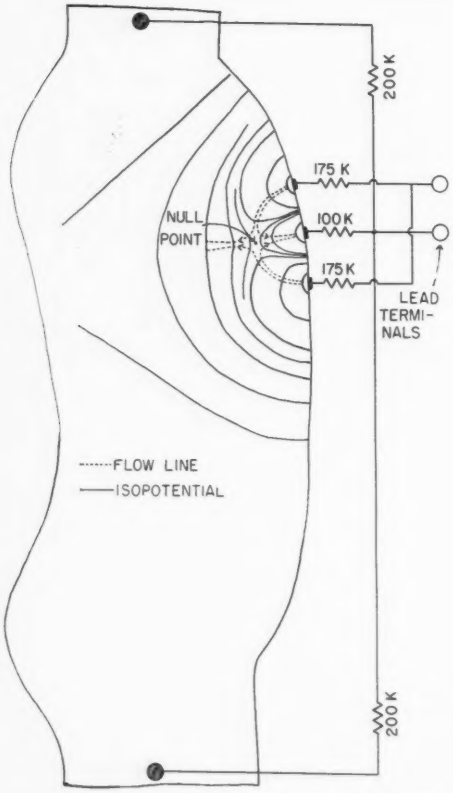

FIG. 4. Isopotential pattern of "null lead" obtained from conducting paper mannikin.

easy to measure the lead field produced on the chest surface over the heart, and there is no question that this field reflects (to an unknown extent, unfortunately) the field within the heart itself. Such measurements can be made either by determining the potential differences produced on the chest when a current is introduced into the lead, or by measuring the voltage produced in the lead when a current is introduced into the same pair of electrodes on the chest. The reciprocity theorem insures that the same reading will result no matter which procedure is followed. Experiments of the second kind have been described by Wilson, Bryant and Johnston,[5] and experiments of the first kind have been performed, but apparently not reported, by Schmitt and Levine.[6]

Some of the data obtained by Wilson and his associates is shown in figure 5. The arrows

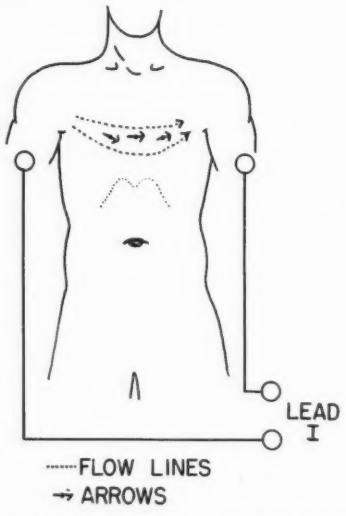

FIG. 5. Arrows show directions of lead I lead vectors at chest surface as determined by Wilson, Bryant and Johnston.[5]

in this figure represent the measured intensity and direction of the surface potential gradient at the central points of the arrows. In figure 5 the flow lines (dashed lines) of the field have been sketched with the intensity and direction of the arrows in mind. It is assumed here that the resistance of the chest surface is the same regardless of the direction of the current flow (isotropic). If this were not so, the direction of the current flow lines would deviate somewhat, in general, from the direction of the potential gradient.

The central terminal leads have also been studied by investigating the fields produced on the chest surface. A series of unpublished experiments were performed by one of the authors (R. M.) in which the fall in potential about the exploring electrode was measured when it and the central terminal were connected to a source of current. These experiments were difficult to interpret because the potential did not drop off completely uniformly on all sides of the exploring electrode, but rather exhibited irregularities of as much as 25 per cent. These were apparently due to variations of conductivity produced by the underlying ribs. When measurements on four sides of the electrode were averaged, they

ndicated that there was some tendency for the urrent to stay near the surface. This could e accounted for theoretically by a layer of igh resistance tissue starting a centimeter or so below the surface of the skin. This might be expected from the presence of ribs and subcutaneous fat. Subsequent studies with fluid mappers[4] indicated that the influence of these layers on the field in the heart was not likely to be great.

Three-Dimensional Approaches

Mathematical Models. No matter how complex the shape of the body or the variations in its conductivity, it is possible, in principle, to find the field of a lead by mathematical methods. In most cases, however, it is much easier to construct an electrolytic model and make measurements on it than it is to attempt such an analysis. It is only when one is interested in relatively general aspects of the field that the use of mathematical models is justified.

An example of a situation of this sort was given in the first paper of this series, where the infinite homogeneous conductor was used as a model for studying the accuracy of interpreting the central terminal chest leads as "heart vector" leads. Its use might be justified by the fact that the difference between the ideal field associated with the interpretation and the actual field is probably considerably greater than the difference between the actual field and the field in the model, at least when the exploring electrode is close to the heart.

The mathematical approach is also useful in studying the over-all characteristics of leads. For example, the interesting properties of the rather unusual leads shown in figure 6 ("null" leads) may be investigated by assuming that the part of the body underneath the plane of the chest surface extends to infinity and is, in addition, homogeneous. This assumption leads to the following analysis.

When a source of current is connected to the lead shown in figure 6*A*, the current streams into the conductor through electrodes A and C, and out through electrodes B and D. Along the line perpendicular to the plane of the electrodes, which passes through the center

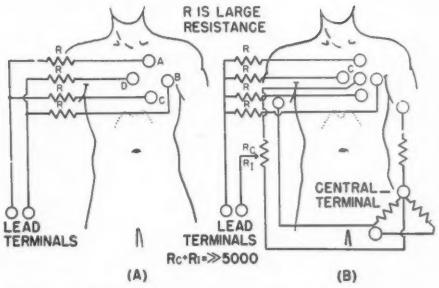

Fig. 6. Electrode and resistor arrangements for "null leads." (*A*) Null along line; (*B*) null at point.

of the square formed by them, the net current is zero, since the electrodes are so arranged that their contributions to the current flowing along or across this line cancel each other. The result of this is that *the lead is insensitive to electromotive forces existing at points along this line.*

More or less the same thing happens when the lead shown in figure 6*B* is used, except that in this case the null occurs at only one point on the center line. As shown in appendix II, the distance d of this point from the surface of the conductor is related to the ratio of the resistances R_c and R_I, and the distance r from the center to the outside electrodes by the equation

$$\frac{R_C}{R_I} = \left(1 + \frac{r^2}{d^2}\right)^{3/2} - 1 \qquad (1)$$

This equation can be used to adjust the ratio of R_c to R_I so that it will give a null in the field at a certain depth and thus be insensitive to electromotive forces at that point. The two-dimensional approximation to the field of this lead is shown in figure 4.

A practical, clinical version of the "null line" and "null point" leads just described can be constructed by attaching five electrodes to a single frame which can be freely moved about on the surface of the chest, and by using the central terminal as an indifferent electrode. The extent to which the actual fields would differ from the ideal fields in the semi-infinite homogeneous conductor depends upon many factors, such as the spacing of the electrodes, the effects of the ribs and subcutaneous fat, the relative resistance of the blood, heart

muscle and lung. However, it seems quite likely that in general the nulls of the leads would occur more or less at the locations predicted in the preceding analysis. An electrode arrangement of this sort might prove useful in the location of recent infarcts. One would start with the "null line" arrangement (fig. 6*A*) and move the electrode frame about until a position for it is found that eliminates the QRS, RS-T segment or T-wave change in the electrocardiogram due to the infarct. (At this position rotation of the frame about the center should produce no change in the part of the ventricular complex under investigation.) Next, one would change to the "null point" arrangement (fig. 6*B*) and adjust the ratio of R_c to R_I until the abnormality due to the infarct again disappears. If the infarct is small, and the field of the lead reasonably like its theoretic model, the infarct should then be located directly beneath the center of the electrode frame at a depth corresponding to the ratio of R_I and R_c that yields a "null."*

Another example of the use of mathematical models in studying lead fields is the analysis of the homogeneous sphere, which has been reported recently by Wilson and Bayley.[7] It is interesting to note that had Wilson and Bayley used the concept of the lead field in their analysis, rather than attempting to find the field of a dipole, they would have obtained the desired result with considerably less effort.

Cadavers, Phantoms and Catheters. Although it is not possible to measure potential differences produced in the heart tissue of a normal human subject, such experiments can be performed with a cadaver, or with an artificial electrolytic model of the body, such as the "phantom" of Burger and van Milaan.[8] Furthermore, as Dr. Frank Wilson suggested to the authors several years ago, it is possible to get a general idea of the field produced in the ventricular cavity of a normal subject by using a catheter equipped with suitable electrodes. These three methods all require a similar type of electrical measurement, and before discussing their advantages and disadvantages a few words about these measurements are desirable.

The general procedure involved is this. A source of current is connected to the lead and the voltage produced between a pair of electrodes on or in the body is measured. Although this procedure sounds simple, experience has shown that enormous errors can result from almost imperceptible mistakes in technic.† One simple procedure which avoids many such pitfalls is the following. A high voltage battery (45 to 180 volts) is used as a current source. It is put in series with a high resistance (50,000 ohms or more) which maintains the current constant, regardless of polarization or variation of contact resistance at the electrodes. (This method of obtaining constant current is well known; see, for example, reference 9.) The current is monitored with an accurate milliammeter and turned off and on with a telegraph key. To insure that there is no leakage of current over undesirable paths, the battery is placed on a dry insulated platform, and the key operated only by the insulated knob. An electrocardiograph employing a mirror galvanometer, preferably battery powered, is used to measure voltage. Its record permits accurate measurement of the deflections and the high-input impedance minimizes the effect of high-contact resistance and polarization on the part of the electrodes connected to the machine. Battery power enables the electrocardiograph to be operated without a ground, thus avoiding the consequences of improper "differential" action on the part of the amplifiers.‡ Records of the calibration voltage of the electrocardiograph are obtained with each measurement of the voltage produced by the lead field.

The pickup electrodes employed should be

* It is theoretically possible for there to be distributions of electromotive forces within the heart which do not set up localized "injury potentials" yet which nevertheless appear as infarcts on the electrocardiographic record. However, such distributions are physiologically improbable, if not impossible.

† The two main sources of trouble are (1) sensitivity of the amplifiers to the "common mode" as well as the "differential" component of the input signal and (2) flow of current through the "ground" electrode.

‡ If the electrocardiograph is line powered, the ground should be put near the pickup electrodes connected to its input.

as small as possible, and their spacing be many times their maximum diameter. If they were large and closely spaced, their effective separation and relative orientation might differ considerably from that expected as a result of variations in contact resistance and polarization of the electrode surfaces.

Two tests should be made before every set of measurements. First, the two wires of the current source are connected to one terminal of the lead and the switch (telegraph key) turned on and off. *The electrocardiograph beam should not be deflected.* Next, the current source is reconnected to both of its electrodes, and the two wires of the electrocardiograph are attached to one of the pickup electrodes. Again, no deflection should be produced when the source is switched on and off. If there is a deflection in either case it is definite proof that the electrical setup is improper, and that there will be errors in the measurements.

Let us now consider some of the merits of the methods of studying lead fields mentioned earlier in this section.

The study of fields in cadavers would be the perfect solution to the problem of determining the fields if it were not for the changes in the resistance of the tissues that occur when circulation ceases, and for the difficulty in inserting the electrodes into the heart muscle without producing significant changes in the resistivity; for example, by the introduction of air in the opening or puncture of the chest and heart tissues.

Numerous experiments with cadavers have been made, the most extensive of which were performed recently by W. denBoer.[9] In these experiments the lead vectors were found by forcing electrodes through the chest wall and measuring the voltages produced in various leads when an alternating voltage was connected through a fairly small resistor to the two electrodes. Considerable data was obtained showing variation of lead vector with location of the electrodes, and from one cadaver to another.

The study of the fields in electrolytic models is considerably easier than experiments involving cadavers, because of the greater ease and reliability of the measurements involved. However, models of this sort may always be criticised (with or without good cause) on the grounds that they fail to mirror exactly the detailed fluctuations of the resistance of the body.

A very simple electrolytic model of the body can be made with a box of some insulating substance such as plastic or glass, and this has been done by Bryant.[10] The length of the tank should be about twice its width. A glass goldfish aquarium with these relative dimensions has been used by the authors. More complex models can be made like those of Burger and van Milaan[8] who, in addition to giving their model lifelike shape, also introduced variations of conductivity by representing the lungs and liver with bags of sand. In the use of electrolytic models, the smaller the electrodes and their spacing, naturally the more detailed the data one can obtain about the field. This data can be most conveniently represented in a simple table of the measurements of the potential gradients in three reference directions at various points in the "heart." Enough measurements should be made to permit accurate interpolations of the values of the components at intermediate points.

Perhaps the most exact method for studying lead fields is by intracardiac leads through the use of catheters. In this case it is certain that the resistivity of the various organs and the shape of the body are correct. However, experiments of this sort are the most difficult to make and to interpret, particularly when a detailed picture of the field is desired. In addition, the measurements concern the field in the cavities of the heart, rather than in the muscle itself, where the electromotive forces are generated.

One experiment of this sort has been reported in the literature.[11] Here, the current was introduced into the two electrodes on the tip of the catheter, rather than into the lead, a technic which may involve the risk of ventricular fibrillation, and should be cautiously used for this reason.

The following procedure would seem preferable. A catheter is obtained which has one electrode on its tip and another three to five centimeters behind it. This catheter is inserted

into one of the ventricles and the position of the two electrodes found by means of x-ray films in the frontal and sagittal planes. (The spacing of the electrodes determined from x-ray pictures must be corrected for the flare of the x-ray beam.) Then a current of from 1 to 5 milliamperes is introduced into each of the leads being investigated and the resultant potential differences between the catheter electrodes measured with a vacuum tube electrocardiograph. Next, the procedure is repeated, with the catheter electrodes in a position as nearly as possible perpendicular to their axis in the first case. Finally, the procedure is again repeated, with the catheter electrodes in a position nearly perpendicular to the plane of the first two axes. The deflections measured this way, when properly calibrated and inserted into the formulas given in appendix III, will yield the three components of the average potential gradient in the cavity where the catheter was located. The lead field current is determined by finding the specific conductivity of the blood and multiplying the potential gradient by it.

An alternate procedure requires the construction of a catheter with four electrodes, so spaced that when the end of the catheter is curled up in the cavity the fourth electrode completes one turn.* If this is done, only one set of x-ray photographs is required, and the catheter need not be moved after it is first put into position. The formulas in appendix III may also be used in this case.

A more detailed picture of the field in the cavity can be obtained with a catheter having more than four electrodes.

In concluding this section on the use of cadavers, phantoms and catheters, it might be pointed out that the various technics can be combined. For example, by putting the excised heart of a cadaver into an electrolytic tank one can obtain more easily than with an entire cadaver a detailed picture of the field within the heart muscle itself, particularly since the resistivity of the latter probably does not change a great deal with failure of circulation. Again, the field within the ventricular cavity of a cadaver can be studied, using the catheter technics. Or again, the procedure discussed earlier for mapping the potential differences on the chest surface might be applied to both cadavers and normal subjects with the object of showing up in this way some differences in the resistivity of cadavers and normal subjects.†

* The end should be curled up in a helix, such as is formed by the thread of a screw. The distance between turns (pitch) should be somewhat greater than half the diameter of the helix.

Discussion

None of the different methods for the study of leads and their fields outlined above have been extensively used, but alone or in combination they are powerful tools for the investigation of electrocardiographic leads and much has been learned from them.

For example, evidence suggesting that the Einthoven triangle concept is sufficiently accurate for clinical purposes has come from the work by Burger and van Milaan[8] on their "phantom," from the catheter studies of Butterworth and Thorpe,[11] and from the work employing fluid mappers reported by McFee and associates.[4] The authors do not believe that the vectors calculated by the use of the Einthoven triangle are exact but think they are fairly close to the true vectors. Some additional evidence supporting this view is provided by calculations carried out from patterns obtained with fluid mappers according to the general method described in the first paper of this series.[1]

These calculations indicate that the Einthoven triangle method is approximately 77 per cent accurate. Readers who are interested in the details of these computations may get them from one of the authors (R. M.).

Although most cardiologists now believe that the central terminal is the best "indifferent" electrode currently available, this view is not held by all. Furthermore, there is little information concerning the situations or conditions under which the central terminal may provide an excellent indifferent electrode and those where it may not be entirely satisfactory.

† This procedure can also be used to test electrolytic models.

Study of lead fields that exist when the central terminal is employed have already been informative. Fluid mappers have been particularly useful.[4] An analysis of the accuracy[1] of the central terminal arrangement was carried out on the fluid mapper pattern shown in figure 3*A* of this paper. This was done by the method outlined in appendix I and indicated an accuracy of 92.5 per cent for this particular lead.

Although the Einthoven triangle scheme may be used to determine the components of the heart vector in the frontal plane with reasonable accuracy, all leads commonly used at the moment to obtain the sagittal component of the heart vector appear to be unsatisfactory. (See fig. 2 and associated discussion.) Our studies indicate that there is only one type of lead which can be used for this purpose. It will be described in the third paper of this series.

In recent years many investigators have attempted to find whether or not different leads were alike by comparing records of the voltages produced in them by the heart. This method of studying leads may sometimes prove to be very unreliable. The electrical forces of the heart may be such that voltages in leads with dissimilar fields turn out to be alike. For example, if the direction of the heart vector were to remain vertical throughout the beat then the voltages in leads I and II would be alike, even though the leads themselves are quite different. For this reason, we feel that definite conclusions about the nature of leads should not be based solely on studies comparing voltages in different leads.

Summary

This paper, the second of three which deal with the study of electrocardiographic leads primarily from the electrical point of view, contains a brief discussion of a number of experimental and theoretic technics which may be used for determining the field of a given lead. The importance of such fields has been pointed out in the first paper of this series.

Methods to obtain patterns representing two-dimensional approximations of the fields are considered first. It is shown how simple sketches, based upon one's intuitive understanding of the field, will quickly reveal the general character of the lead. Such sketches are used to point out the shortcomings of several leads which have been used to obtain the sagittal component of the heart vector. Special devices for studying two-dimensional fields, such as "fluid mappers," are then discussed briefly.

Methods of obtaining information about the actual three-dimensional fields are considered next. The use of simple mathematical models is illustrated by the analysis of a new type of lead which is insensitive to electromotive forces at certain locations. The procedure for calculating the general direction of the field from measurements of the voltage produced between the electrodes of a catheter is described in detail.

APPENDIX I

Quantitative Calculations from Flow-Line Patterns

The relative intensities of the field at different points in a two-dimensional flow-line pattern can be determined by measuring the spacing of the lines, since this spacing varies inversely with the intensity of the current flowing between the lines; that is, if the spacing is halved the current intensity is doubled. This is due to the fact that the current flowing between any two lines remains constant, regardless of the spacing.

If a line going from one part of the field to an adjacent point is perpendicular to the direction of the current flowing between them, then there will be no potential difference between the points, since there is no component of current to create a voltage drop in that direction. If a whole series of points are connected to adjacent points by lines perpendicular to the current flowing between them, the line that is formed is called an "isopotential." When any flow line and isopotential cross, they are always at right angles to each other. The isopotentials may be used in place of the flow lines to determine the direction of the current flow, since it is known that the latter are always perpendicular to the isopotential lines. The spacing between adjacent isopotentials also varies inversely with the intensity of the current passing from one to the other, provided that the resistance of the medium is constant. The reason for this is that closely spaced lines indicate a rapid change in voltage, and this, by Ohm's law, is accompanied by a correspondingly intense current.

Consider now the determination of the relative intensity of the current at *two different points* in the heart due to the field of the *same* lead. One begins with a flow-line pattern of the lead under considera-

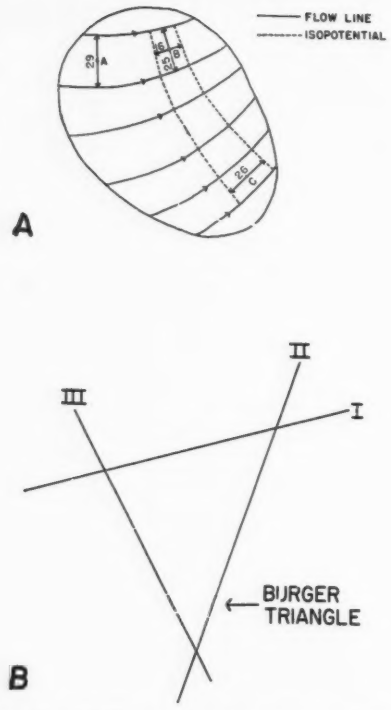

FIG. 7. (*A*) Sketch demonstrating quantitative analysis of a flow line pattern. (*B*) Sketch showing that if the directions of the lead vectors of the standard leads are known, then their relative magnitudes can also be determined.

tion, such as that shown in figure 7*A*, which represents lead I. From this pattern the isopotentials of the field are constructed by joining adjacent flow lines with short straight lines in such a fashion that these segments are perpendicular, or as nearly so as possible, to the flow lines at both ends. (If the flow lines are converging the isopotential segment should form equal interior angles with the two flow lines terminating it.) The relative intensity of the current at points A and C is found with the aid of a third point B, which lies between the same flow lines as A, and the same isopotentials as C. Measurement of the spacing of the flow lines shows that the current at B is 1.16 times as intense as the current at A. Similarly, measurement of the isopotential spacing shows that the intensity of the current at C is .62 times that of the current at B. It follows that the current at C is .73 times the strength of the current at A.

It is also possible to calculate the relative intensities of the fields produced *at the same point* by *two different leads*. However, this can be done conveniently only with leads that have one electrode in common. The flow-line patterns of the lead fields must first be obtained for each of the leads and for the third lead formed by the two electrodes which the leads do not share. It was shown in the first paper of this series that the vectors representing the fields of these three leads will add together at any point in such a fashion that they form a ("Burger") triangle. If the directions of the flow lines for the three different leads are known, the shape of the triangle can be found by the construction illustrated in figure 7*B*. Once the shape of the triangle has been found, the relative intensities of the currents represented by the different sides of the triangle are obtained by measuring the relative lengths of the sides.

APPENDIX II

The "Null Point" Lead

Although this lead actually consists of five electrodes, its symmetry is such that the null may be calculated from the arrangement shown in figure 8. Here the current enters the chest surface via electrodes A and B and leaves it via electrode C and infinity. It is not difficult to show that each of these electrodes will have the same field associated with it that it would have if in an infinite medium, except that it will be twice as strong. Along the center line the intensities of the three currents are thus given by the equations

$$|\vec{J}_A| = |\vec{J}_B| = 2\,\frac{1}{4\pi}\cdot\frac{(1/2)}{r^2+d^2} = \frac{1}{4\pi}\cdot\frac{1}{r^2+d^2} \qquad (1)$$

$$|\vec{J}_C| = 2\,\frac{1}{4\pi}\,\frac{I_C}{d^2} = \frac{1}{2\pi}\,\frac{I_C}{d^2}. \qquad (2)$$

$\vec{J}_A$ and $\vec{J}_B$ have together a resultant directed opposite to $\vec{J}_C$ whose strength is given by

$$|\vec{J}_A + \vec{J}_B| = 2\,\frac{1}{4\pi}\cdot\frac{1}{r^2+d^2}\cos\theta = \frac{1}{2\pi}\cdot\frac{1}{r^2+d^2}\cdot\frac{d}{\sqrt{r^2+d^2}}. \qquad (3)$$

If $\vec{J}_C$ is equal and opposite to this resultant, then

$$\frac{I_C}{d^2} = \frac{1}{r^2+d^2}\cdot\frac{d}{\sqrt{r^2+d^2}}. \qquad (4)$$

That is

$$\frac{1}{I_C^2} = (r^2+d^2)^3/d^6 \qquad (5)$$

or

$$\frac{1}{I_C} = \sqrt{\left(1+\frac{r^2}{d^2}\right)^3}. \qquad (6)$$

This equation gives the fraction of the lead field current which must leave the conductor via the central electrode in order for there to be a null at a

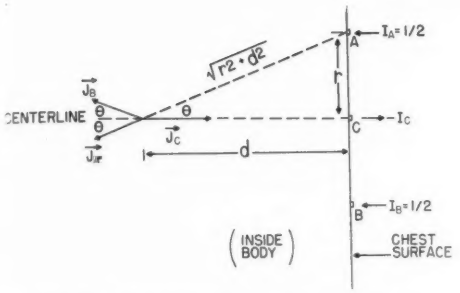

FIG. 8. Null point lead. (See appendix III)

depth d. The other portion $(1 - I_C)$ of this current leaves the conductor via the electrode at infinity.

If the central electrode and the electrode at infinity are connected to the positive terminal of the lead via resistors R_C and R_I, respectively, then the unit current will divide according to the equation

$$I_C = \frac{1/R_C}{1/R_C + 1/R_I} = \frac{R_I}{R_C + R_I} \tag{7}$$

providing that the resistors are very large in comparison with resistance between the electrodes. Substituting this in equation 6, the result is

$$\frac{R_C}{R_I} = \sqrt{\left(1 + \frac{r^2}{d^2}\right)^3} - 1. \tag{8}$$

APPENDIX III

Determining the General Direction of the Field from Catheter Measurements

The general direction of the field within the heart can be estimated from three measurements if it is assumed that the field is uniform. In this case the voltage produced between two electrodes of the catheter will be given by the equation

$$V = p\vec{J} \cdot \vec{L} = pJ_V L_V + pJ_T L_T + pJ_S L_S \tag{1}$$

where J_V, J_T and J_S are the vertical, transverse and sagittal components of the lead field current density $\vec{J}$; L_V, L_T and L_S are the corresponding components of the line $\vec{L}$ separating the two electrodes of the catheter, and p is the specific resistivity of the medium. This equation simply states that the voltage between the catheter electrodes will be proportional to (a) the projection of the lead field voltage gradient on the line joining the electrodes, and (b) the distance between the electrodes. If the orientation of the catheter is now changed, the equation will become

$$V' = p\vec{J} \cdot \vec{L}' = pJ_V L_V' + pJ_T L_T' + pJ_S L_S' \tag{2}$$

where the prime symbols represent the new voltage and x-ray measurements resulting from the change in the orientation of the catheter. When the position of the catheter is changed for the third time, then

$$V'' = p\vec{J} \cdot \vec{L}'' = pJ_V L_V'' + pJ_T L_T'' + pJ_S L_S''. \tag{3}$$

Now, if the three voltages v, v' and v'' are measured, and if L, $\vec{L}'$ and $\vec{L}''$, representing the positions of the catheter electrodes are found from side and frontal x-rays, these factors, combined with the measurable value of the specific resistivity p of blood will enable the three simultaneous equations 1, 2, 3 to be solved for the three unknown components of the lead field $\vec{J}_v$, $\vec{J}_t$ and $\vec{J}_s$. The equations that result are

$$I_V = \frac{1}{PD}[V(L_T' L_S'' - L_T'' L_S') - V'(L_T L_S'' - L_T'' L_S) + V''(L_T L_S' - L_T' L_S)] \tag{4}$$

$$I_T = \frac{1}{PD}[-V(L_V' L_S'' - L_V'' L_S') + V'(L_V L_S'' - L_V'' L_S) - V''(L_V L_S' - L_V' L_S)] \tag{5}$$

$$J_S = \frac{1}{PD}[V(L_V' L_T'' - L_V'' L_T') - V'(L_V L_T'' - L_V'' L_T) + V''(L_V L_T' - L_V' L_T)] \tag{6}$$

where

$$D = L_V(L_T' L_S'' - L_T'' L_S') - L_T(L_V' L_S'' - L_V'' L_S') + L_S(L_V' L_T'' - L_V'' L_T')$$

SUMARIO ESPAÑOL

Este informe, el segundo de tres que tratan sobre el estudio de derivaciones electrocardiográficas principalmente desde el punto de vista eléctrico, contiene una breve discusión del número de técnicas experimentales y teóricas que pueden usarse para determinar el campo de una derivación dada. La importancia de estos campos fué señalada en el primer informe de esta serie.

Métodos para obtener patrones representando aproximaciones en dos dimensiones de los campos se consideran primero. Se demuestra como sencillos bocetos, basados en el modo de ver intuitivo del campo, pueden revelar prontamente las características generales de la derivación. Estos bocetos se usan para señalar los defectos de ciertas derivaciones que han sido usadas para obtener el componente sagital del vector cardíaco. Diseños especiales para estudiar campos en dos dimensiones, tales como "fluid mappers", se discuten brevemente.

Métodos para obtener información sobre los

campos en tres dimensiones se consideran después. El uso de modelos matemáticos sencillos se ilustra por medio del analisis de un nuevo tipo de derivación el cual es insensitivo a fuerzas electromotrices en ciertas posiciones. El procedimiento para calcular la dirección general del campo de las medidas de voltaje producidas entre los electrodos de un cateter se describe en detalle.

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A Study of the Spatial Vectorcardiogram of the Ventricular Gradient

By G. E. Burch, M.D., J. A. Abildskov, M.D., and J. A. Cronvich, M.S.

A concept of the ventricular gradient as a quantity which varies with time during the cardiac cycle is presented. Some methods for deriving values of the "mean instantaneous ventricular gradient" and from these the "vector-cardiogram of the gradient" are outlined. Despite obvious shortcomings in these technics, some results of the application of these methods are reported.

PROBABLY one of the most important contributions among the many made by F. N. Wilson and his associates[1] was the introduction of the concept of the ventricular gradient. Ashman[2-5] and Bayley[6] were responsible for excellent developments of this concept and extended its clinical applications. These and other observers have limited their studies to what might be termed the mean ventricular gradient, primarily because of the nature of its derivation. Differences in the time course of the processes of depolarization and repolarization influence the form of the electrocardiogram. The ventricular gradient, as measured from the electrocardiogram, indicates in a single vector *the mean difference in duration of the excited state*[1] or, as defined by Ashman,[2] *the net electrical effect of the differences in time course of the processes of depolarization and repolarization.* The ventricular gradient is considered to be a single vector quantity which defines the mean difference in magnitude and direction of the duration of the excited state and of the electric potential therefrom for the entire electrical cycle of a heart beat. The vector defining the gradient is directed from the area in which the mean duration of the excited state is greatest to the area in which the mean duration is least. The frontal plane projection of the gradient has been studied most extensively, but relatively little attention has been given to the spatial gradient. Indirect studies of the spatial ventricular gradient[4] have been made by observing the gradient in the frontal plane as calculated from the standard limb leads. Obviously, such indirect studies of the mean spatial ventricular gradient are subject to limitations. This report is concerned primarily with the spatial ventricular gradient and especially with the "spatial vectorcardiogram of the ventricular gradient" determined from leads recorded from a spatial reference frame.

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The Concept

The Hypothetic Cell. When a single cell (fig. 1) suspended in a volume conductor is activated by a stimulus applied as indicated, the wave of depolarization progresses from right to left (observer's left to right) and a depolarization wave, R, is recorded by a galvanometer from the point, P, outside the cell. If the system is homogeneous chemically and physically and if the process of repolarization begins where depolarization began and proceeds at the same rate as did depolarization, a repolarization wave, T, of the form shown is recorded from point, P. The areas enclosed by R and T are equal but opposite in sign. From Wilson's concept of the gradient, it is obvious that, if all parts of the cell remain in the excited state for the same length of time, the algebraic sum of the areas enclosed by R and T is zero. Thus there are no variations in the time course of

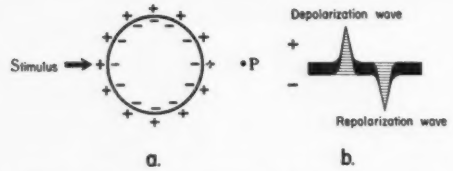


FIG. 1. Hypothetic example of no gradient. The duration of the excited state is equal throughout the cell.

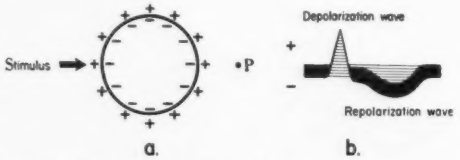


FIG. 2. Hypothetic example in which the gradient is zero. Even though the duration of the excited state varies throughout the cell, the average external electrical effect is zero.

depolarization and repolarization and no electrical effect which such variations would produce. Therefore, no gradient exists in this case.

A curve with greater similarity to the human electrocardiogram would result if the rate of repolarization were considerably less than that of depolarization and if repolarization occurred simultaneously at several points on the cell. This would result in a repolarization wave of lower voltage than the depolarization wave. Such a wave is shown in figure 2. In this case the duration of the excited state has not been the same in all parts of the cell, yet the areas enclosed by the depolarization and the repolarization waves are equal. Therefore, the mean or net electrical effect from variations in the time course of depolarization and repolarization is again zero. It is this *net* electrical effect which is calculated from the electrocardiogram. This may be termed a condition with a zero gradient as contrasted with the situation described previously in which no gradient exists.

Figure 3 shows a cell which has been made nonhomogeneous by cooling its right half to 15 C. A stimulus, S, applied at the site indicated in figure 3*a*, evokes a wave of depolarization, R, and one of repolarization, T, as shown in figure 3*b*. However, because of the cooling, repolarization begins not where depolarization

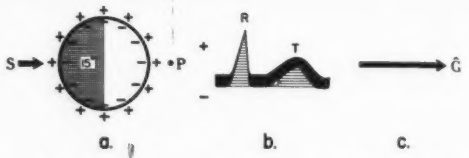


FIG. 3. Hypothetic example in which gradient exists. The duration of the excited state varies throughout the cell to produce an external net electrical effect.

started but on the opposite, uncooled half, where the chemical and physical reactions constituting repolarization take place more rapidly because of the warmer environment. The duration of the excited state differs in different parts of the cell, being longer at the site of stimulation on the cooled half and shorter on the opposite or warmer half. Thus, there is a difference in the time course of depolarization and repolarization such that the net electrical effect of this difference is not zero. The net sum of the areas enclosed by the depolarization wave, R, and repolarization wave, T, is positive. Thus, a "ventricular" gradient for the cell exists in this instance, and the gradient is represented by the mean vector quantity, $\hat{G}$ (fig. 3*c*). The vector is directed from the area of greatest mean duration of the excited state to the area of least mean duration. The magnitude of the vector, expressed in microvolt-seconds (μvs), is an expression of *both* the mean *magnitude* of the difference in *duration of the excited state* for the cell and the *magnitude* of the *net electrical effects produced by the difference in the time course of the processes of depolarization and repolarization.* Previous publications[1-6] may be consulted for a more detailed presentation of the concept of the ventricular gradient.

The Human Heart. The heart is a syncytium of striated muscle and is not made up of discrete or distinct cells. Furthermore, the ventricle is activated not from a single point but from *different points* at *different times.* Likewise the heart is not a closed sphere but essentially two irregular hemispheres, auricles and ventricles. These three differences produce complexities not inherent in the hypothetic cell discussed earlier. Furthermore, when the ventricular gradient is calculated from the human

lectrocardiogram, at least the following three ssumptions are made:

1. The magnitudes of the resting potential cross the muscle membranes are equal hroughout the myocardium.

2. The degrees of depolarization or reversal of dipoles during the accession wave are equal throughout the myocardium.

3. The rates of depolarization are equal throughout the myocardium.

It is extremely unlikely that these assumptions hold at all times, especially in the presence of cardiac disease. Should they not hold, they will be responsible for net electrical effects as calculated by the method introduced by Wilson and his associates for determination of the ventricular gradient. These net electrical effects are not due to differences in the time course of the processes of depolarization and repolarization and, therefore, should not be included in calculations of the ventricular gradient. However, because of the more or less arbitrary nature of the calculations and of possible failure to satisfy the three assumptions, measurements of the ventricular gradient are limited in accuracy. For example, errors would exist whenever currents of injury are present. Nevertheless, in spite of these errors and our limited knowledge and technics for measuring such errors, much can be learned about electrical events in the heart from a study of the ventricular gradient. Therefore, it is advisable to continue with these discussions and studies of the gradient.

The human heart may be considered to be made of many small local areas of muscle each of which has its own gradient. These areas may be of variable size. Each local area may be compared with the hypothetic cell described previously. For example, the septum of the heart is apparently depolarized first on its left, superior and posterior portion (fig. 4*a*), most probably because the left bundle divides earlier and delivers a stimulus there first. Likewise, the septum will probably repolarize first or at least before the conus area or the posterior aspect of the free wall of the left ventricle (fig. 4*c*) which is usually depolarized last. Therefore, the septal portion will manifest its local

FIG. 4. Diagram showing areas of ventricular myocardium which are depolarized and probably repolarized initially (*a*) intermedially (*b*) and finally (*c*).

gradient before the localized portion of the posterior part of the free wall of the left ventricle does. The area of the heart near the septum and apex will probably manifest its local gradient sometime between the local sites in figures 4*a* and 4*c*. Thus, one can consider that there are local gradients for portions of the septum, apex and free wall of the left ventricle as well as gradients for many other areas. Certain areas will manifest their gradients simultaneously; whereas, others will manifest theirs at different times during the electrical cycle of the heart. Thus, there are mean ventricular gradients which exist from instant to instant. These may be termed mean instantaneous ventricular gradients. The mean *instantaneous ventricular gradient vectors* may be compared, for purposes of orientation, with the mean instantaneous vectors of the process of depolarization or of repolarization. *Disease processes* within the heart will vary the order of activation of local areas of muscle and, therefore, the resultant mean instantaneous gradients.

The mean instantaneous ventricular gradients are *spatial* vectors. They indicate how the spatially oriented net electrical effects due to differences in the time course of the processes of depolarization and repolarization varied from site to site in the three-dimensional myocardium. Up to the present, no attempt has been made to study the variations in the mean instantaneous ventricular gradient. Only the algebraic sum of these, the *mean ventricular* gradient, $\hat{G}$, has been studied.

Despite the existing limitations in knowledge and technics, an attempt has been made in the remainder of this paper to present the results

of efforts to study the variations of the "mean instantaneous spatial ventricular gradient."

The Spatial Vectorcardiogram of the Ventricular Gradient, the G $s\hat{E}$-loop

Attempts were made to construct the spatial loop of the ventricular gradient, (G $s\hat{E}$-loop), using selected electrocardiograms and vectorcardiograms. The limitations in accuracy and application of the methods are obvious. Some of these will be indicated. Two types of electrocardiograms and vectorcardiograms were employed.

1. *Selected Tracings without T Complexes.* If one accepts the method introduced by Wilson and associates for calculating the mean spatial ventricular gradient from $s\hat{A}_{QRS}$ and $s\hat{A}_T$ (1), then $s\hat{G} = s\hat{A}_{QRS}$ whenever $s\hat{A}_T$ is zero, or $s\hat{G} = s\hat{A}_T$ whenever $s\hat{A}_{QRS}$ is zero. In such cases the G $s\hat{E}$-loop has the same configuration as the QRS or T $s\hat{E}$-loop, respectively. The latter type of electrocardiograms is extremely rare. However, electrocardiograms in which the T wave is, for practical purposes, isoelectric in the three standard limb leads are not unusual. In such cases the projections of $s\hat{G}$ and of $s\hat{A}_{QRS}$ on the frontal plane of the body are identical. Occasionally electrocardiograms are encountered in which the T waves are for practical purposes isoelectric in the precordial leads as well. Under these circumstances the G $s\hat{E}$-loop has the same spatial configuration as the QRS $s\hat{E}$-loop. Figure 5 shows the latter type of electrocardiogram. When T waves are absent in the standard leads but present in the precordial leads, $s\hat{A}_T$ is projected either perpendicularly away from or toward the frontal plane.

If a spatial vectorcardiogram is obtained in which the spatial loop of the T is zero or essentially zero so that it could be ignored, then the spatial loop of the QRS and the spatial loop of the ventricular gradient are essentially the same. Such a spatial vectorcardiogram is shown

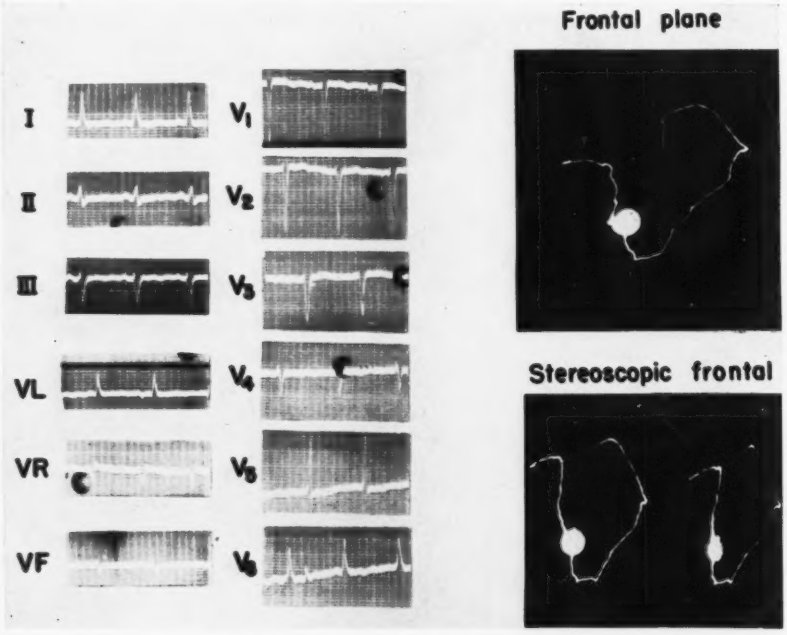


Fig. 5. Electrocardiogram in which T waves are low or essentially isoelectric throughout the standard, unipolar and precordial leads. The frontal plane projection of the spatial vectorcardiogram and stereoscopic views of this projection are shown. The QRS $s\hat{E}$-loop is large, whereas the very small T $s\hat{E}$-loop is lost in the halo at the isopotential point. Because of the small T $s\hat{E}$-loop, the "G $s\hat{E}$-loop" is essentially the same as the QRS $s\hat{E}$-loop. Consult text for details.

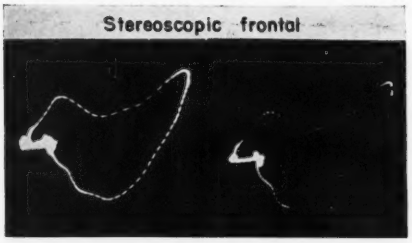


FIG. 6. Stereoscopic view of the frontal plane projection of the spatial vectorcardiogram of a patient with left ventricular hypertrophy. Because the T waves of the electrocardiogram were low in amplitude and enclosed a small area and because the T sÊ-loop was small, the "G sÊ-loop" is similar to the QRS sÊ-loop.

in figure 6 for a patient with severe left ventricular hypertrophy in which the T wave was small in magnitude. Such spatial vectorcardiograms are rarely, if ever, encountered in normal man. They are more often observed in patients with left ventricular hypertrophy. The loop of the gradient is essentially the same in configuration in this instance as the QRS sÊ-loop (fig. 6).

In time, the loop of the gradient begins at some time after the beginning of depolarization and at the beginning of repolarization and ends when repolarization is completed. The duration of the loop of the gradient is equal to the duration of repolarization. For this reason the time lines shown in the QRS sÊ-loop of the vectorcardiogram have no significance when this loop is considered to be the G sÊ-loop.

2. *Selected Tracings in which Both QRS and T Are Present.* It is obvious that this method is limited in its accuracy because of lack of detailed knowledge of the time course of depolarization and repolarization of any heart, and especially that of man with cardiac disease. Because some information, though limited, does exist for the normal heart, this method was applied to 10 normal subjects with type 1 type 2 spatial vectorcardiograms.[7]

In this case we have assumed that the local areas of the myocardium that are depolarized first are also repolarized first. Even though in general this appears likely, it *must be emphasized that it is purely an assumption* with no experimental justification. The first portions of the QRS sÊ-loop and the first portions of the T sÊ-loop are assumed to be derived from essentially the same local segments of myocardium, and the later portions of each loop are produced by accession and regression within the same areas. This is an assumption subject to considerable possibility of error, but it is employed herein as an approach for determining the new instantaneous ventricular gradients and the resultant sÊ-loops. Therefore, a spatial loop of the gradient was calculated by vectorially adding mean instantaneous spatial vectors of the respective loops selected in proper sequence.

After the mean instantaneous spatial vectors of the QRS and T sÊ-loops were selected, they were, with limited justification, added in the following manners: (*A*) With consideration being given only to the magnitude of the QRS and T vectors in millivolts and (*B*) with consideration of the vectors in microvolt-seconds.

A. Figure 7 represents a spatial vectorcardiogram and an electrocardiographic lead recorded for a normal subject. It is evident from the maximal mean instantaneous vector of the T sÊ-loop that this vector corresponds in time with the maximal deflection of the T wave in the electrocardiogram. The interval from the end of the QRS complex to that point of maximal deflection in the T wave was measured.

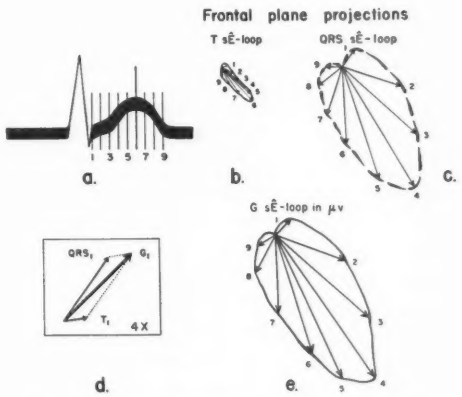
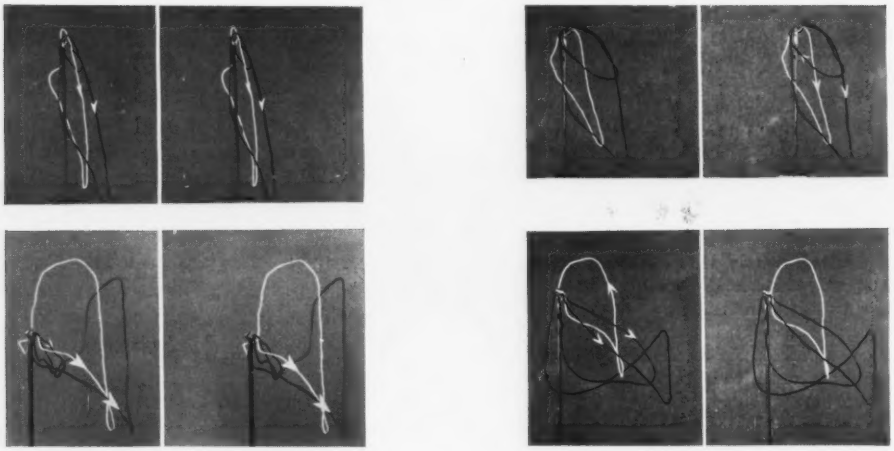


FIG. 7. Method *A* for calculating the plane projections of the "G sÊ-loop" from the plane projections of the spatial vectorcardiogram and the electrocardiogram. Insert *d* is magnified four times. Consult text for details.

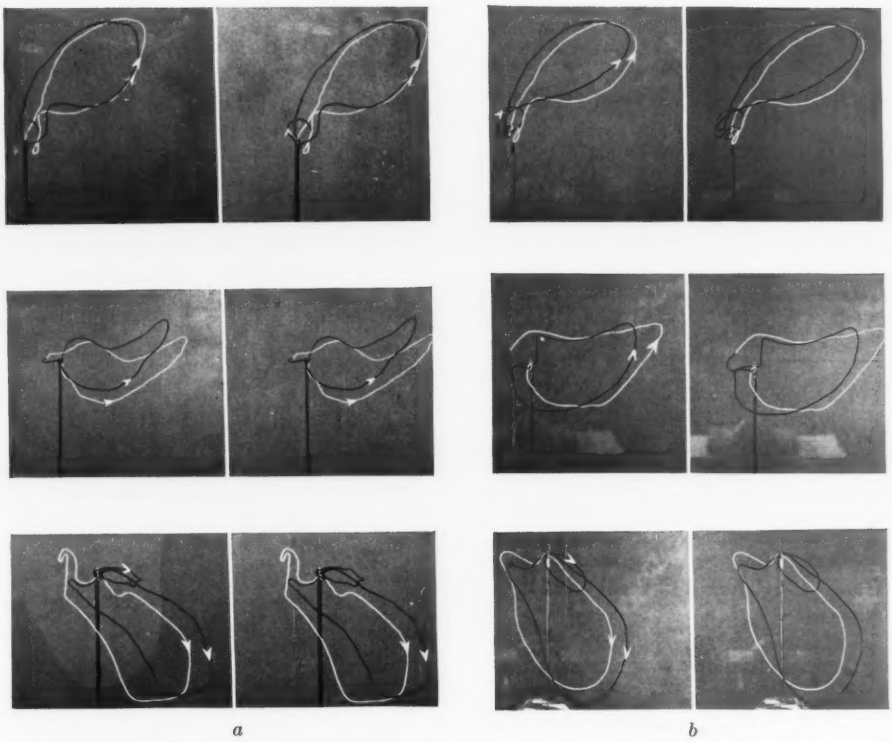


a *b*

FIG. 8. Two normal spatial vectorcardiograms with "G sÊ-loops" calculated in part *a* by the method shown in figure 7 and in part *b* by the method shown in figure 10. These are photographs of wire models, the respective pairs of which will stereoscope if held at a proper distance (approximately 10 inches) from the eyes. Numbers 1*a* and *b* were from a subject with a type 1 pattern. Numbers 2*a* and *b* were from a type 2 pattern. In this illustration and in figure 9 the QRS sÊ-loops are the white loops, the G sÊ-loops are the large black loops and the T sÊ-loops are the smaller black loops. The attached arrow heads indicate the direction of rotation of the loops.

This represented the duration of the efferent limb of the T sÊ-loop and the ascending limb of the T wave. The number of 0.02-second intervals for the ascending limb of the T wave was counted. Then the efferent limb of the T sÊ-loop was divided into that number of segments of equal length. The duration of the descending limb of the T wave of the electrocardiogram was then measured, and the number of 0.02-second intervals was counted for this limb. The afferent limb of the T sÊ-loop was divided into that number of segments of equal length. The total number of unit divisions obtained for the T sÊ-loop was recorded. The QRS sÊ-loop was then divided into the same number of time intervals of equal duration as there were total divisions made for the T sÊ-loop. The interrupted time lines in the trace of the QRS sÊ-loop were employed as a guide for proper time-distribution of the divisions in the QRS sÊ-loop, since the cathode ray spot moved at varying speeds during the recording of the traces. Consult figure 7 for the distribution of the time intervals. Mean instantaneous vectors were then drawn from the isopotential point to the respective intervals marked on the respective QRS and T sÊ-loops. When this was completed, the respective mean instantaneous vector quantities of the QRS sÊ-loop and T sÊ-loop were added vectorially in sequence, the resultant of each addition being considered the "mean instantaneous spatial ventricular gradient." The termini of the mean instantaneous gradients were connected sequentially to complete the trace of the "spatial loop" of the ventricular gradient. Figure 8*a* shows two normal "G sÊ-loops" calculated by this method. Several "G sÊ-loops" were calculated by this method for subjects with cardiac disease; three are shown in figure 9*a*.

The records were selected carefully so as to make the analysis as simple as possible. Vectorcardiograms were selected which had relatively little halo at the isopotential point and in which the interruptions (600 per second) on the trace were particularly good and usually readily discernible even near the isopotential point. Furthermore, the T sÊ-loops were such that the maximal mean instantaneous vector corresponded satisfactorily with the point of maximal amplitude of the T waves in the electrocardiogram. In the case of subjects with cardiac



a *b*

FIG. 9. Two spatial vectorcardiograms (1 and 2) of subjects with left ventricular hypertrophy and one (3) of a subject with right bundle branch block with "G sÊ-loops" calculated in part *a* by the method shown in figure 7 and in part *b* by the method shown in figure 10.

disease, tracings were selected in which the T sÊ-loops were particularly small or negligible compared with the magnitude of the vectors forming the QRS sÊ-loop. In fact, in some cases the T sÊ-loop could be ignored, and the G sÊ-loop calculated in this fashion was, for all practical purposes, the same as the QRS sÊ-loop (fig. 9*a*).

It is evident that the analyses conducted in this fashion fail to result in "gradient quantities" of the same unit value as those described by Wilson and his associates. The loops derived by this arbitrary method could be made to include a representation of time by varying the density of the line outlining the G sÊ-loop in proportion to the variations in duration of the respective portions of the QRS and T sÊ-loops from which the gradient sÊ-loop was derived.

B. Because the gradient as defined by Wilson is obtained from the areas enclosed by the respective complexes of the electrocardiogram, a "vectorcardiogram" of the gradient which has a closer relationship to that definition was derived from quantities which include voltage variations with time (microvolt-seconds). This method of derivation, shown in figure 10, was the same as outlined in the preceding section for method *A* except that the magnitude of each mean instantaneous vector was modified by an appropriate time factor to convert it to microvolt-seconds. For example, in figure 10 if each time interval represented in the T wave was 0.02 second, the respective vectors in microvolts in the T sÊ-loop were multiplied by 0.02 second to convert them to microvolt-seconds. The respective vectors of the QRS sÊ-loop were multiplied by the time interval in seconds between each of them to convert them to microvolt-seconds. The resultant mean instantaneous vectors of the QRS and T sÊ-

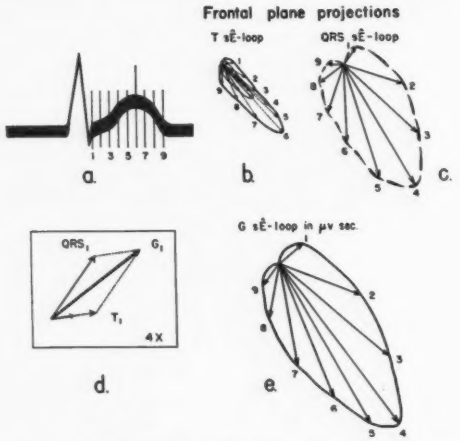


FIG. 10. Method *B* for calculating the plane projections of the "G sÊ-loops" from the plane projections of the spatial vectorcardiogram and electrocardiogram. The areas enclosed by the QRS and T complexes of the electrocardiogram are considered in this method. Insert *d* is magnified four times. Consult text for details.

loops expressed in microvolt-seconds were then added vectorially to obtain a series of mean instantaneous vectors of the "gradient." Their termini were connected to produce a G sÊ-loop. Examples are shown as companion illustrations (b-parts) of figures 8 and 9.

DISCUSSION

It is probable that the G sÊ-loops derived in this study are only approximations of the true moment-to-moment variations of the spatial orientation of the ventricular gradient. It is not possible with existing knowledge and techniques to record correctly the time-course of the spatial variations in the ventricular gradient. It is evident, however, that the mean ventricular gradient, as usually determined, fails to depict the details of spatial changes of the gradient during the electrical cycle of the heart beat. Should more detailed recording of G sÊ-loops become possible it would probably provide important information.

It is also evident that the method of determining the gradient described by Wilson and associates requires that all depolarization and repolarization be completed before the calculation can be applied. This provides the mean gradient for the entire myocardium. Until local areas of the myocardium can be studied adequately, the G sÊ-loop will offer little assistance in understanding the electrical events of the heart beat. The concept of the ventricular gradient presented by Wilson and associates applied to the ventricular muscle as a whole. However, this concept of the gradient could be applied to *local* areas in the myocardium. These may be termed *local gradients*. The over-all gradient of any mass of muscle with local gradients may be termed the *generalized gradient*. Then there are the over-all *mean ventricular gradient*, which has been considered previously, and the *mean instantaneous ventricular gradient*, a concept of which has been developed in this paper. There are the *spatial gradient*, mean or mean instantaneous, and the various *plane projections* of the spatial gradient vectors with all of which this paper is concerned. Finally, there is the loop of the gradient, spatial (G sÊ-loop) or various plane projections (G Ê-loop). Other classifications are possible but will not be presented in detail here. Just as these concepts apply to the ventricular gradient, so they may apply as well to the *auricular gradient*, for, like the ventricular musculature, the auricular musculature has gradients.

SUMMARY

A concept of the spatial vectorcardiogram of the ventricular gradient is discussed. Spatial loops of the gradient (G sÊ-loops) have been calculated by two methods. The limitations of this and other concepts of the gradient and the errors in calculations are discussed. The importance of extending the concept of the ventricular gradient to include local and general gradients as well as mean and mean instantaneous gradients for the myocardium of the ventricles is indicated. It is also pointed out that the same concepts apply to the myocardium of the auricles.

SUMARIO ESPAÑOL

El concepto de la pendiente ventricular como una cantidad que varía con el tiempo durante el ciclo cardíaco se presenta. Algunos de los

métodos para derivar los valores del "promedio instantáneo de la pendiente ventricular" y de estos el "vectorcardiograma de la pendiente" se esbozan. No obstante defectos obvios en estas técnicas, algunos de los resultados de las aplicaciones de estos métodos se informan.

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Mechanical Inscription of the Vectorcardiogram

By A. Calhoun Witham, M.D., and Wm. F. Hamilton, Ph.D.

A modification of the vectorcardiographic method of studying electrical events is presented. Simultaneous scalar leads, taken by any vector lead system, are first recorded. The important time intervals, difficult or impossible to read from the loop itself, are measured from these tracings. Proper pairs of the scalar leads can then be rapidly integrated into vector loops by an easily constructed drawing board based on the pulley system. This instrument is described in detail. It is demonstrated that loops so derived do not appear to differ in their important characteristics from electronically integrated loops.

THE CLINICAL usefulness of the vectorcardiogram is most obviously limited by its inability to record satisfactorily temporal relationships such as P-R and Q-T intervals, heart rate, and types of irregularity. Practical considerations, such as a heavy investment in expensive electronic equipment, processing time, and the need of trained personnel also restrict its use. It is believed that the method to be described will adequately answer these objections until the higher frequency deflections, not recordable on direct-writing apparatus or in mechanically inscribed loops are proven to be of diagnostic importance.

The first requirement is a two-channel recording electrocardiograph with a paper speed of at least 50 mm. per second. The scalar electrocardiograms so recorded may be used for determining the important time relationships referred to above. The choice of a vectorcardiographic lead system may be left to the discretion or bias of the investigator. All such systems currently in vogue have electrodes so placed that the scalar components in any plane allegedly record along axes at right angles to each other. The magnetic plates which deflect the beam of electrons in the cathode ray tube are, therefore, at right angles. This same geometric principle has been utilized in designing a drawing board by means of which a vector loop can be derived from a pair of simultaneously recorded electrocardiograms. A writing point is deflected by two chains, pulling it along two axes at right angles. Each chain is attached through a pulley system to a pointer which traces the scalar electrocardiograms.

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Description of Apparatus

Figure 1 illustrates the complete device. The choice of materials is to some extent arbitrary. The baseboard of our model is of $\frac{5}{8}$ inch plywood. A 12 inch square plate of $\frac{1}{8}$ inch plexiglass is screwed to this as a drawing board since the soft plywood is otherwise pitted by constant pecking with a sharp pencil point. The 1 inch square blocks (1–7, fig. 1) on which the pulleys are mounted were cut from brass square stock. The pulleys were machined from $\frac{3}{4}$ inch brass round stock and are set on washers so as to turn freely. The beaded chain* connecting the pencil holder (S) and tracing arms (W) is $\frac{1}{16}$ inch and moves easily in the pulleys. Both chains are 36 inches long and have an adjustable coupling attaching a 9 inch length of No. 000 Brass safety chain, whose links will fit the eye hooks on the stylus. This arrangement permits varying the effective length of the bead chain as necessary simply by catching the adjustable couple at any point.

The pencil holder or guide (S) is a $1\frac{1}{2}$ inch length of plexiglass round stock bored to fit loosely the size pencil to be used. A $2\frac{1}{2}$ by $2\frac{1}{2}$ inch plate of $\frac{1}{16}$ inch plexiglass is cemented

* Bead Chain Co., Bridgeport, Conn.

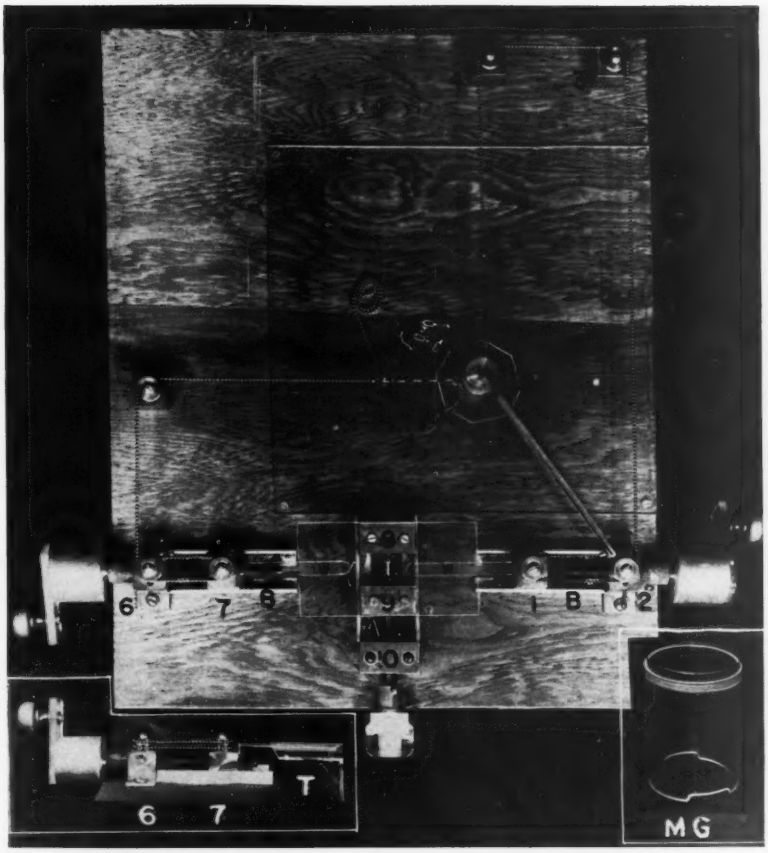

FIG. 1. Drawing board described in text. Left inset shows profile of tracing arms. Chain is arranged around pulleys to give the pencil holder a 4 to 1 mechanical advantage over the tracing arms. Both tracing arms are similar. Right inset shows magnifying glass set in plexiglass cylinder to make alignment of electrocardiogram and tracing arms easier.

to the bottom of the stylus to give it stability, and a small hole, large enough to admit a pencil point, is bored in its center. Two ¼ inch eye screws are screwed into the stylus at right angles to which the link chain is hooked. A third eye screw bisects the remaining angle on the stylus, and a heavy rubber band keeps the chains taut by stretching between the third eye screw and pulley block 2. The band can be attached to the same screw that anchors the bead chain.

The scanning table (T) to which the electrocardiograms are fastened with Scotch tape, is supported by blocks 8 and 9, 1⅞ inches long, and cut from 1 inch square brass stock. The table itself is 5½ by 3 inches and of ⅛ inch plexiglass, and is screwed to each brass block by two flat-head screws. This carriage is guided by a track made of two ½ inch aluminum angles 4 inches long. Block 10 is stationary and is bored to fit a ½ inch brass rod (A) threaded 13 threads to the inch. Half inch round brass collars lock this rod to blocks 9 and 8 so that turning the attached plastic handle moves the entire carriage along the track.

The pointers (W) are of 1/16 inch plexiglass ⅜ by 3⅜ inches. A tiny hole is made about 3/16 inch from the end and filled with india ink, and these dots are used for precise alignment of the arm with the electrocardiogram

under it. The pointers are screwed to a ⅛ inch plastic plate which is screwed to blocks 1 and 7 (left inset, fig. 1). Blocks 2 and 6 are fixed to the baseboard and act as a bearing for the screws B which, when turned, move the pointers at right angles to the edge of the scanning table. The ends of the bead chain are anchored in blocks 2 and 6 by screws and a coupling ring. The chains are looped around one or two pair of pulleys, depending upon whether one wishes the motion of the pointers to be amplified two or four times at the pencil guide (left inset, fig. 1). The blocks 1 and 7 to which the pointers are attached run in tracks of the same ½ inch aluminum angles. Plastic handles are attached to the shaft of the screws B with a No. 10 set screw. The traversing nuts (blocks 1 and 7) must be closely fitted to the guide rails throughout this length to avoid play. These two rails must be carefully aligned with each other and at right angles to the direction of travel of the scanning table. Cost of materials does not exceed $12.00 and mechanical skill required for construction is minimal. For these reasons, it is preferred to the device described by Shillingford and Brigden[1] for the same purpose but which requires a light source and optical system.

Use of Apparatus

One cycle of a two-lead electrocardiogram is clipped out and attached to the scanning table with Scotch tape. A piece of paper on which the loop is to be drawn is aligned with the edge of the plexiglass drawing board and fastened in place with Scotch tape. The length of the two chains is adjusted so that they impinge on the pencil guide at right angles and are held taut by the pull of the rubber band. The last vertical time line on the electrocardiographic record which crosses both simultaneously recorded tracings before ventricular electrical activity has begun is moved under the two dots on the pointers by moving the scanning table. Each pointer is then moved so that the black dots overlie the exact spot where the tracings cross the time line. A pencil mark is made through the hole in the pencil guide to mark the zero point of the QRS loop. The scanning table is then moved until the black dots touch the next time line. The pointers are adjusted as before and the first movement of the loop indicated by a second pencil mark. At equal time intervals the process is repeated until both electrocardiograms have returned to the baseline and the QRS loop is completed. The setting of the pointers must always be made by moving them in from the

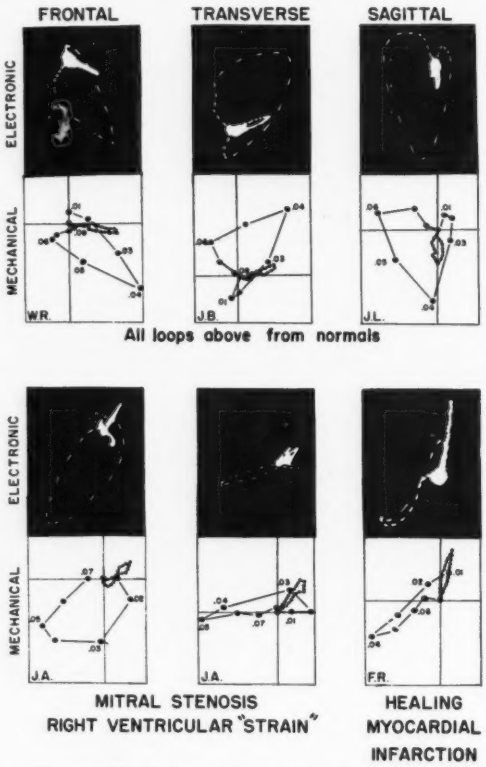

Fig. 2. The interruptions of the electronic loops occur every 0.004 second, and the direction of rotation is indicated by the sharp end of the light streaks. The dots in the mechanical QRS loops are at .01 second intervals and the T loop is indicated by a beaded line. The pairs to be examined are adjusted to the same approximate size to facilitate comparison. P loop is omitted on mechanical tracings. The orientation of all loops in the same plane is similar: (1) Frontal: the patient's left is on the reader's right. (2) Transverse: anterior chest is towards bottom of illustration and patient's left is on the reader's right. (3) Sagittal: anterior chest is on the reader's right.

same direction to avoid lag as the pencil guide changes direction. The procedure is then continued until the T loop is also completed. We have found a paper speed of 50 mm. per second with readings on and half way between the vertical time lines (.01 second intervals) adequate speed to record the characteristic shape, clinically important vectors, and direction of rotation of the majority of loops. Finally, a vertical and horizontal axis is drawn through the zero point to establish a reference system and the successive points numbered and connected with straight lines. The average time required, after some practice, is about seven minutes per loop.

Figure 2 demonstrates a comparison between six loops electronically recorded (kindly supplied by Dr. William F. Milnor of Johns Hopkins University) and their counterparts mechanically derived by the method just described. The same scalar leads were used for both electronic and mechanical integrations. In every case it is seen that the direction of rotation, general shape, and orientation of the loops are about as close as any successively recorded vectorcardiogram cycles.

Limitations of the Method

Since only one-fourth as many points are recorded in the above mechanically derived loops, slight, brief changes in direction and magnitude are not reproduced. The significance of these changes, however, is still unknown.[2]

Since each component of each vector is recorded, not as a straight line, but as an arc on the circumference of a wide circle with blocks 4 and 5 their center and their radius the length of chain between these blocks and the stylus, each vector direction is slightly distorted and its magnitude shortened. The larger the component, the greater amount of the circle it will involve and consequently the greater the inaccuracy. On the other hand, errors on the two arcs are opposite in direction and tend to cancel each other. Figure 2 confirms that this is not a serious defect.

If vectors of no shorter duration than .01 second are traced, the peak of a tracing may occasionally be bracketed by the arbitrarily chosen points and the maximum extent of the loop not drawn. This is easily recognized during transcription, however, and the missing peak may be included in the loop with an approximate timing of the event.

In practice, different colors are used for the zero point, for the QRS, and for the ST-T loops, and the points are lightly numbered as they are written to avoid confusion.

Some care must also be exercised in selecting complexes to be used. The one chosen should not include a shifting baseline, and the initial vectors from two complexes from the same patient will not be reproducible unless the take-off of the QRS always bears the same temporal relationship to the last time line while the electrocardiogram is still isopotential.

Actually the mechanical loops present one advantage over some electronically integrated photographed loops in that the P, QRS, and T loops can be artificially separated so that superimposition of the three, which sometimes makes it difficult to read the initial and terminal QRS forces, is eliminated. Experience has shown that students seem to grasp the significance of the vector loop more quickly when the integrative process can be visualized.

Summary

A simple, inexpensive, easily built mechanical device for integrating two simultaneously recorded electrocardiograms into a vector loop is described. It is demonstrated that the loops so derived bear a close relationship in their important features to those electronically written and photographically recorded.

Sumario Español

Una modificación del método vectorcardiográfico de estudiar los acontecimientos eléctricos se presenta. Derivaciones escalares simultáneas, tomadas por cualquier sistema de derivaciones vectoriales, son por primera vez registradas. Los intervalos de tiempo importantes, dificiles o imposibles de leer de la misma onda, se miden en estos trazados. Pares propios de derivaciones escalares pueden ser rapidamente integrados a ondas vectores por

medio de una tabla de dibujo facilmente construida y basada en un sistema de poleas. Este instrumento se describe en detalle. Se demuestra que ondas obtenidas de esta manera no aparecen diferir en sus características importantes de ondas electronicamente integradas.

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Acceleration Ballistocardiography

Design, Construction, and Application of a New Instrument

By Robert V. Elliott, M.D., Robert Gay Packard, Ph.D., and Demos T. Kyrazis

The construction of a linear accelerometer for use in ballistocardiography is presented including the relationship between acceleration, displacement, and velocity. The sensing element described is new in the field of ballistocardiography, being based on an electrochemical principle. A means of easily calibrating the instrument is described, thereby allowing quantitative measurements of various components of the ballistocardiogram. Tracings of one abnormal and two normal individuals are illustrated to show the relationship between displacement and acceleration.

BALLISTOCARDIOGRAPHY has been established as a valuable diagnostic aid in the evaluation of a great number of cardiovascular conditions. Many types of recording apparatus are now available. They fall into two general categories, namely, the moving table type[1-3] and the portable, direct body type.[4-9] The moving table types have proved to be accurate instruments, but their great disadvantage is that the apparatus is bulky and complex. Most of the direct body types operate on the displacement or velocity principle and yield tracings which are excellent for qualitative analysis. However, because of the very principle upon which these instruments develop their electrical current, which is in turn amplified and recorded as the familiar ballistocardiogram, they fail to measure quantitatively the component of the ballistocardiogram which is theoretically the most important, namely, the force of movement imparted to the entire body by the recoil of the heart and the impact of the blood ejected from the heart.

The velocity pickup generates its electrical current by the passage of electromagnets through a fixed magnetic field, and the electrical current generated is directly proportional to the velocity of the body. Consequently, the amplitude of any of the waves is more a measurement of the time interval over which the force is applied and is not an accurate measurement of force. Similarly, with the displacement type pickup, the amplitude of the waves obtained is dependent upon how far the body is moved by the force but does not measure accurately the force which caused the movement. Standardization of either form of ballistocardiograph is difficult and at present is not available for general use.

Arbeit and Lindner[10] and Smith and Bryan[11] have recently devised an apparatus with which they differentiate velocity electrically into acceleration and integrate velocity into displacement, obtaining the so-called differentiated acceleration tracing.

When acceleration is differentiated from velocity, and velocity is difficult to standardize, it appears that the calibration of differentiated acceleration would be very difficult and perhaps unreliable. There are as yet no other feasible methods of obtaining acceleration tracings, except for the instruments based on the seismic principle. Since accurate measurements obtained by seismic instruments depend on a rather large mass, delicately suspended in a sphere or box, their size precludes use directly on the body, and they are not sensitive in the range of forces which are encountered in ballistocardiography.

Since force can be calculated from acceleration it seems that the ideal instrument for general use in ballistocardiography would be an accelerometer which is rugged, portable, inexpensive, and which could record on an electrocardiograph as does the Dock (electromagnetic) Ballistograph.[8] This instrument should be capable of accurately measuring acceleration entirely independently of velocity

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or displacement. It should be sensitive to forces in the range from 0.00 to 0.02 g and have the ability to follow changes in direction of acceleration (from head to foot, side to side, or from anterior to posterior) very rapidly. In addition, the apparatus should be linear in its response and should be capable of measuring acceleration rather than merely changes in acceleration. It should be capable of simple calibration, preferably by the use of the 1 millivolt standardization of the electrocardiograph machine, thereby eliminating additional equipment which is often cumbersome and subject to its own critical standards. With such an instrument anyone possessing an electrocardiograph could take ballistocardiograms directly from a patient, and by presetting the sensitivity to a previously determined 1-millivolt deflection, could read the ballistocardiogram in terms of force. This would mean an accurate quantitative evaluation of the ballistocardiogram in a comparable manner to that now used in electrocardiography.

We have been able to construct an instrument that is capable of a flat response from 0 to 3000 cycles per second (without capacitance in the circuit) and shows a linear response from 0 to 0.015 g forces and above. It reproduces the typical ballistocardiogram in its gross contour and is capable of recording consistent small deflections in the systolic pattern not seen in the smooth record of the velocity or displacement type apparatus. These changes will be described in more detail below.

This accelerometer is an electrokinetic device whose operation is determined by electrical changes at the surfaces of contact of a mercury-sulfuric acid interface, the so-called "U effect." The general theory of the "U effect" is given in several papers by Ueda and others[12, 13] and is summarized briefly in an interesting manner by Yeager and Hovorka.[14] Although the theory is beyond the scope of this paper, the construction of this apparatus is amazingly simple. The actual pickup consists merely of a capillary tube with alternate layers of metallic mercury and 1 normal sulfuric acid, thereby creating multiple interfaces of mercury and electrolyte solution. At each end of the capillary a mercury seal is employed into which a small copper or platinum electrode is inserted and in turn sealed to the capillary tube. Upon movement such an element produces electrical voltage by changes of the surfaces of the mercury and electrolyte solution, the voltage being proportional to the change of contour of these interfaces. The element responds maximally to acceleration in its longitudinal axis, and this electrical output can be transferred directly to the recording apparatus (electrocardiograph) through the right arm and left arm electrode leads with the selector switch on lead I. A filtering system can be used in the circuit to filter out high frequency waves, but this is not necessary. This element is mounted on a cross bar between the shins of the patient with the element lying in an exactly level position in the longitudinal axis of the body. The standard leg block, as used in the velocity and displacement type pickups, is utilized in facilitating the mounting of this apparatus, and, of course, a solid table for the patient is essential as in the other portable type pickups.

The element is easily calibrated with respect to its response to a known force by means of a pendulum. By adjusting the sensitivity control of the electrocardiograph to a desired valley-to-peak deflection, and then in turn noting the deflection of the stylus upon the introduction of 1 millivolt into the electrical circuit, a constant reproducible record of force can be obtained at will by merely presetting the sensitivity control to this desired deflection of the stylus.

Polarization of the element is readily accomplished during standardization on the pendulum while periodic motion is taking place. By arbitrarily calling one direction of the pendulum "headward" and the other "footward," the deflection of the recording stylus can be noted with each direction. It must be noted, however, that when properly polarized in this fashion the pendulum direction called "headward" causes the stylus to show a downward deflection, which, on first consideration would lead one to the assumption that the apparatus is polarized in reverse. Upon careful consideration, however, it must be recalled that this element is a true accelerometer, and it is the electrical output of the mercury and electrolyte interfaces that

we wish to record and not the movement of the capillary tube. Consequently, a "headward" movement of the tube causes a "footward" movement of the interfaces because of the inertia of the liquid within the capillary, and actually we record the mirror image of displacement or a minus sine wave pattern in contrast to the sine wave of displacement. With the apparatus calibrated in this manner, the typical gross pattern of the systolic component of the ballistocardiogram is recorded from the body with the J wave being the prominent headward deflection and the K wave being the prominent footward deflection.

Design, Construction, and Calibration

The above described capillary tube with the mercury and sulphuric acid interfaces is mounted perpendicular to a cross piece containing a series of capacitors in parallel leading to a suitable connection for the electrode leads from the electrocardiograph. A rotor switch allows selection of capacitances varying from 0 to 0.009 microfarad for use as desired in filtering out high-frequency vibration.

Construction of Capillary Element

The exact inside diameter of the capillary tube is relatively unimportant since each element is calibrated according to its output characteristics when subjected to known forces. However, the stability of the element is proportional to the diameter of the capillary tube. Tubes of smaller diameter are more stable than those of large diameter because of the capillary attraction phenomenon. The ideal inside diameter appears to be in the vicinity of 0.3 to 0.5 mm., and such capillary tubes are easily drawn by hand from soft glass tubing. Thick-walled capillary tubing can also be used if the inside diameter is not too great. In addition, to the stability factor, the smaller the diameter (within certain limits), the greater the electrical output per number of interfaces.

After cutting off one end of the glass tube, leaving at least 20 to 25 cm. of capillary attached to the other end of the glass tubing, a 90 degree angle is made near the distal tip of the capillary tube. The capillary is now ready for "loading." We have found it best to "load" capillaries in a horizontal position through the small tip by suction with a syringe from the large end of the tubing. A 1 cc. tuberculin syringe, mounted on a stand, is satisfactory for this. A fine control of the suction facilitates loading, and this can be accomplished by bolting a plate to the plunger of the syringe and in turn connecting this plate to a micrometer screw. The large end of the capillary tube is attached to the tip of the

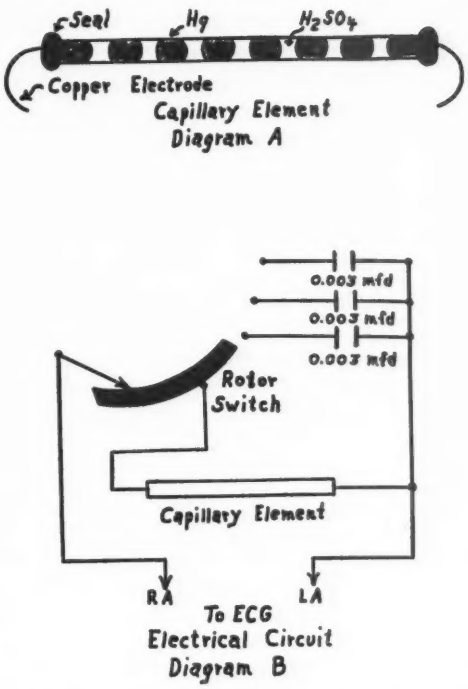

FIG. 1. *Diagram A:* Capillary tubing filled with alternate layers of mercury and normal sulfuric acid, thereby creating multiple mercury-acid interfaces. Care should be taken to avoid any gas bubbles in this element. *Diagram B:* Electrical circuit of the acceleration ballistocardiograph. Shielding of element not shown in the diagram.

syringe by means of plastic or rubber tubing, care being taken to approximate the glass tubing and the tip of the syringe as closely as possible, thereby allowing little play in this connection. At the tip of the capillary tube, a small cup half filled with metallic mercury and half filled with normal sulfuric acid is placed. By gently swinging the tip of the capillary tube alternately in and out of the mercury meniscus, and simultaneously creating a negative pressure in the capillary tube by the use of the micrometer screw, alternate layers of mercury and sulfuric acid can be drawn into the capillary tube.

It is best to preload the syringe and capillary tube with normal sulfuric acid to eliminate the compression and expansion properties of a gaseous medium which tend to make negative pressure difficult to control. When the tube has been "loaded" to the desired length, and with the desired number of mercury cellules, a sealing wax seal is applied to the tip of the tube following its removal from the cup. (A length of capillary tube approximately 13 to 15 cm. in length, containing approximately 25 to

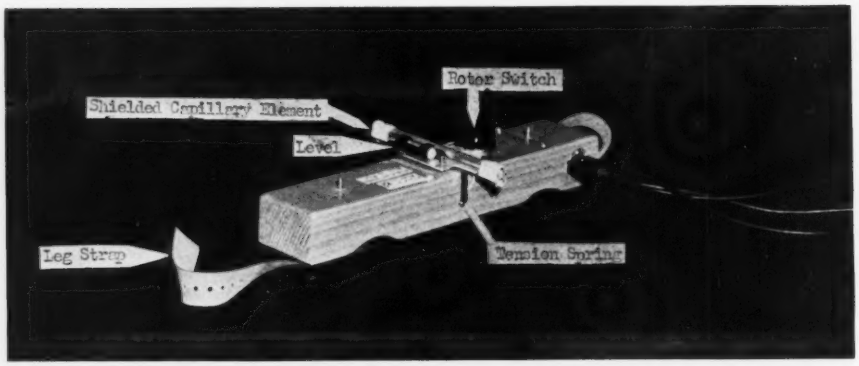

FIG. 2. Portable (leg type) acceleration ballistocardiograph. Note the hinged plate on which the shielded element is mounted, allowing exact leveling by means of a set screw.

40 cellules of mercury, appears to be adequate for ballistocardiography.) When this has been accomplished, the "loaded" tube may be cut at its desired length near the proximal end, and a small copper wire electrode inserted into the large mercury cellule and again sealed with sealing wax or suitable substance. The distal limit of the element is then measured, cut, and the above process of inserting a copper electrode is repeated, and the element is finished. (See fig. 1, diagram A.)

Construction of the Acceleration Ballistocardiograph

The cross piece can be designed of metal, plastic, or wood. Additive capacitors in parallel are embedded in the cross piece, and connected to a rotor switch, which allows selection of the desired capacitance ranging from 0 to 0.009 microfarad with 0.0015 or 0.003 microfarad gradations. A three pole plug is mounted for connection of the two electrode leads from the electrocardiograph and a grounding wire. The electrical circuit is diagrammed in figure 1, diagram B.

The capillary tube is next enclosed in a cylindric aluminum or copper shield, which is connected to a ground wire. This shield is advisable to prevent the possibility of picking up alternating current interference from surrounding electrical fixtures and also affords protection against breakage of the glass tube. Grounding has been found necessary because the capillary element produces an electrical potential and is capable of acting as an antenna for electrical frequencies if unshielded and exposed. The shielded element is mounted to a cross piece on a hinged plate, with a tension spring and set screw adjustment at the end of the plate opposite from the hinge for exact leveling of the element in the horizontal plane. The cross piece is grooved on its bottom surface to cradle comfortably on the shins and is strapped into a fixed position in a snug, but not tight manner by means of rubber tapes (fig. 2).

Calibration of the Acceleration Ballistocardiograph

As mentioned above, an accurate calibration can be accomplished with regard to g forces by the use of a pendulum. The pendulum can be constructed by use of a heavy solid platform (approximately 6 by 8 by ¼ inch steel or brass) mounted from each of its four corners by fine piano wire. The ballistocardiograph is placed on the pendulum with the element in a horizontal position with its long axis in the longitudinal swing of the pendulum. A vernier scale, mounted at one end of the platform, allows accurate measurement of the arc of the swing.*

Acceleration thus varies sinusoidally with time for small amplitudes of swing, and the maximum amplitude determines the maximum acceleration. Since the pendulum we use has a length of 25 inches, the displacement of ⅛ inch will give an acceleration of 0.005 g. Knowing this, by use of the vernier scale we can release the pendulum at ⅛ inch from its 0 position, to develop a force of 0.005 g; if the pendulum is released ¼ inch from its 0

* The pendulum we use has a length of 25 inches. If T represents the tension on the supporting wires, mg the weight of the pendulum (the product of mass and acceleration due to gravity), ϕ the angle of the supporting wire from the vertical position, and $mg \tan \phi$ the component of the forces in the horizontal direction, we can set up the following equations for calculation of the force of any swing of the pendulum:

$$f = ma = mg \tan \phi$$

Therefore $a = g \tan \phi$. But for small values of ϕ (when ϕ is expressed in radians) $\tan \phi = \phi$. Therefore, $a = g\phi$. Since ϕ is very nearly equal to d/l (where d represents distance the pendulum moves from its zero position and l represents the length of the pendulum) we have the following: $a = (d/l)g$.

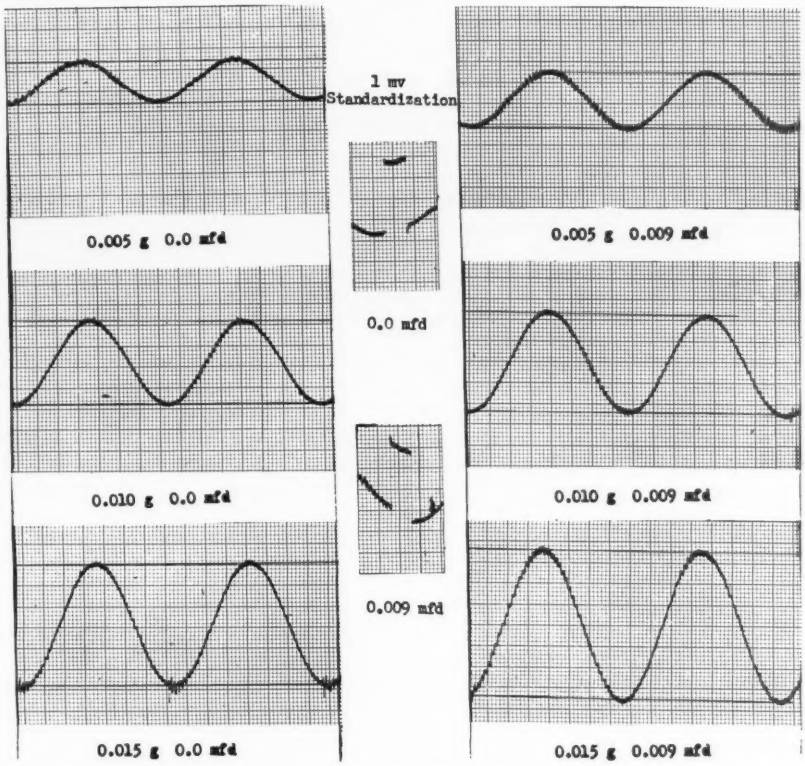

FIG. 3. Response of the acceleration ballistocardiograph to known forces (as delivered by the pendulum). Note the linear response as the force increases. The output is increased with a capacitance of 0.009 microfarad in the circuit, but this in no way affects the linear response. A stylus deflection, from 1 millivolt, of 16 mm. was used in all tracings. The sensitivity setting should be made with the instrument in the circuit. Measurements are made from valley to peak of the seventh cycle; dividing this measurement by two gives the correct deflection from any given force, since the 0 point of the pendulum is midway between the valley and peak deflections.

position, it develops 0.010 g; if the pendulum is released $\frac{3}{8}$ inch from its 0 position, it develops 0.015 g; it will continue to develop an increasing force of 0.005 g for each $\frac{1}{8}$ inch added to its swing. (This linear response applies only within certain limits, but these limits far exceed the forces we measure in ballistocardiography.)

Tracings obtained from this calibrating apparatus, are shown in figure 3. All measurements were taken on the valley-to-peak swingings of the stylus at the seventh cycle of the pendulum. It will be noted that there is a linear response of the acceleration ballistocardiograph with the increasing g forces. It must be noted, however, that calibration of any one element is not the same when different capacitance is used in the circuit. The response for any given capacitance in the circuit does not in any way affect its linearity, but the response from 0.005 g with a 0 microfarad setting and the response to the same force with a 0.009 microfarad setting will differ slightly. This is due to the fact that the element produces its own electrical current, and, with increased capacitance in the circuit, current in the circuit is increased. This fact affects the calibration only slightly on various microfarad settings and can be corrected by merely checking the output of the ballistocardiograph on all microfarad settings, constructing a table of the output differences with each setting, and using this table as a reference when measuring the ballistocardiograms. Once the ballistocardiograph has been calibrated on the pendulum and its response to various forces recorded, no further calibration is necessary by use of the pendulum.*

* The instrument illustrated in figure 2 has maintained a constant output to a given force for a period of eight months, and shows no signs of deterioration

All acceleration tracings illustrated in this paper, were taken with a ballistocardiograph standardized at a valley-to-peak deflection at the seventh cycle of 36 mm. with 0.015 g with a 0.009 microfarad capacitance in the circuit, and the sensitivity control set to a 16 mm. deflection with 1 millivolt. The valley-to-peak measurement represents a total force of 0.030 g, and, therefore, from the 0 point of the pendulum, 0.015 g is equivalent to 18 mm. deflection of the stylus. Therefore, a 1 mm. deflection is equivalent to 0.00085 g. It is a simple matter to convert this measurement into dynes when the weight of the subject is known. $F = ma$ (where force is in dynes, m is the weight of the subject in grams and acceleration is 980 cm. per second^2). Since g may be substituted for a and each millimeter deflection is 0.00085 g, our equation is $F = m\ 0.833$. If we had a subject weighing 154 pounds (70 Kg.) we would have the following equation:

$F = 7000\ (Gm.) \times 0.833$
$F = 58{,}310$ *dynes per millimeter deflection of the stylus*

If we want to measure the force of J_a and its amplitude is 10 mm., it is simply 5.83×10^4 times 10 or 58.3×10^4 dynes. Such measurements can be calculated for either headward or footward deflections.

Discussion

By using the above described instrument on normal individuals and on patients with known cardiac disease we have obtained interesting tracings. Various headward and footward motions that are not seen in displacement and velocity tracings are consistently seen in acceleration tracings made with this instrument. A problem of nomenclature arises in the use of true acceleration ballistocardiograms, not allowing use of the present lettering system, as described by Braunstein.[15] The Committee on Ballistocardiographic Terminology[16] has presently deferred this problem, allowing the possibility of confusion to exist regarding this matter. In an attempt to avoid further confusion, we have used the nomenclature used by Arbeit and Lindner[10] of labeling the prominent headward deflection of acceleration as J_a. The subscript, a, would likewise be appropriately used on H, I, and K waves that correspond in gross *contour* to waves so labeled in displacement and velocity tracings. In such a system of labeling, it is to be noted that J_a occurs simultaneously with I (of displacement). Consequently, it must be kept in mind that the genesis of J_a and J are not the same as would be assumed by such a lettering system.

Since all systolic complexes are not identical, even in the same person, we feel it inadvisable to compare anything other than simultaneous displacement and acceleration ballistocardiograms. We accomplish this by mounting acceleration and electromagnetic ballistographs on a patient's legs at the same time and recording their output simultaneously on a double-channel, direct writing electrocardiograph. We obtained displacement tracings by using a 20 microfarad capacitance in the circuit of a Dock (electromagnetic) Ballistograph, thereby integrating (almost completely) velocity input to a displacement output. The R wave of the electrocardiogram is superimposed for time reference.

Notching of I_a, in subjects considered normal, is a fairly consistent finding, as is notching to biphasic components of H_a. High speed (50 mm. per second) tracings frequently demonstrate notching or slurring of the I_a-J_a limb in normal subjects. Accentuation of these findings is often marked in subjects with heart disease. A clear-cut biphasic component of J_a is at times evident, indicating a very fast change in the body motion (frequently not detected by displacement or velocity tracings). We have further labeled such biphasic waves using the numbers 1 and 2 as subscript.

Of particular value is the ability to quantitate various headward and footward deflections of the acceleration ballistocardiogram. These measurements are made directly from the tracings and allow tracing comparisons from one person to another. It appears that quantitative comparison of wave amplitudes will

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at this writing. The stability of the element depends on several factors (the pH of the acid, the number of interfaces remaining constant, and airtight seal), but these are technical problems that can be overcome with better construction technics now under investigation. The use of soft glass is not advisable, since the acid will change in pH after several weeks and the output will noticeably diminish. Elements of Pyrex tubing have been found to be relatively stable.

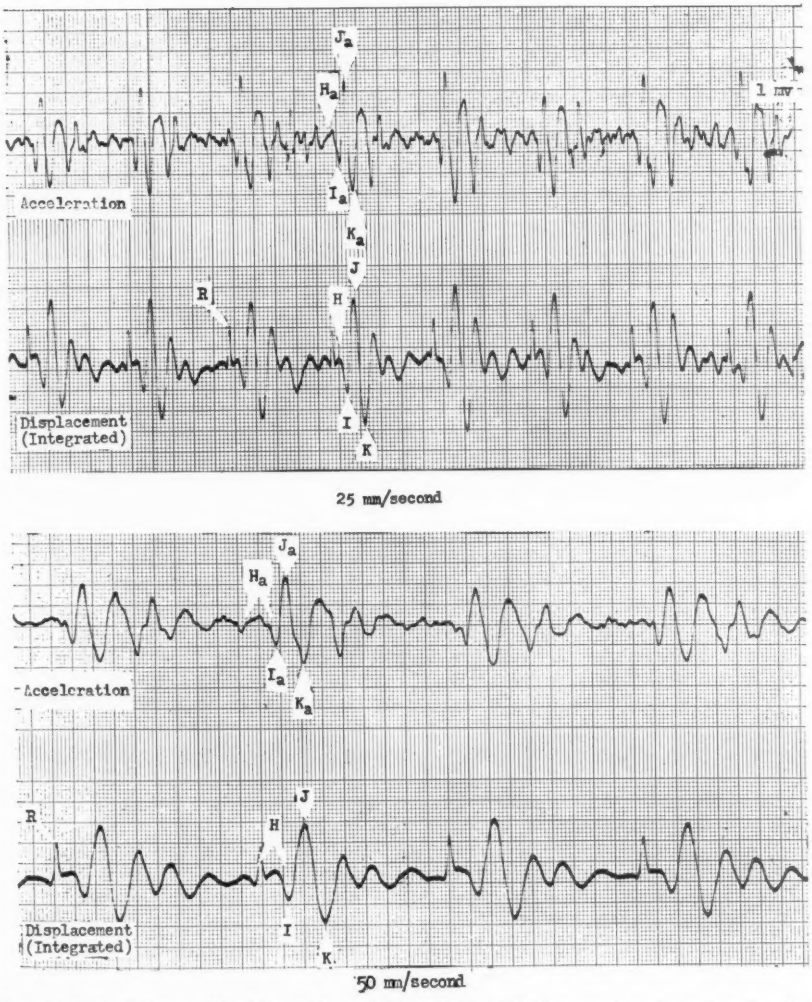

FIG. 4. J. B., 24-year-old white male, weighing 74 Kg. Displacement and acceleration ballistocardiograms are considered normal. Note the notching of the H_a wave, in both the normal and high speed tracings, and that I_a and M_a are greater in amplitude in acceleration tracings. The amplitude of the J_a waves represents 98.6×10^4 dynes during inspiration. Acceleration is seen to be 180 degrees out of phase with velocity.

lead to the establishment of ranges of normality and perhaps be of value in the interpretation of ballistocardiograms.

By quantitative analysis of the cases illustrated, the force in any phase of cardiac systole can be appreciated. If we consider the normal tracings to be representative of expected limits, we find a range of J_a amplitude to vary from 70.6×10^4 to 98.6×10^4 dynes in inspiration, and from 51.3×10^4 to 67.8×10^4 dynes in expiration. By comparison, in the abnormal tracing illustrated, we find the J_a amplitude to represent only 34.4×10^4 dynes in inspiration and 13.7×10^4 dynes in expiration.

Because components of the acceleration

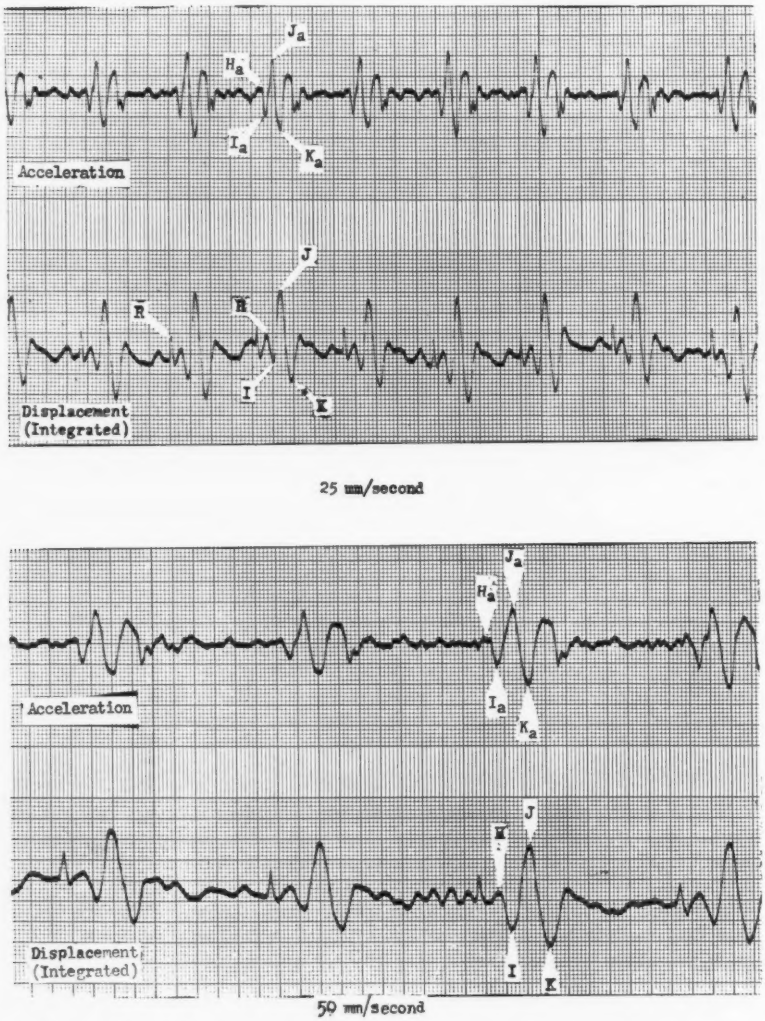

FIG. 5. A. P., 23-year-old white male, weighing 77 Kg. Displacement and acceleration ballistocardiograms are considered normal. The entire systolic complex is of smaller amplitude than in the preceding case, far smaller in terms of actual force than would be expected by comparing displacement tracings on both individuals. The J_a amplitude in inspiration, represents a force of 70.6×10^4 dynes, far less than in the preceding case. Note the slight irregularity of the I_a–J_a limb in the acceleration tracing not seen in the displacement tracings. High-speed tracings reveal this irregularity to be actually a slight notching, still not evident in the displacement tracings.

tracing are multiple and occur very rapidly, we have taken recordings at both standard speed (25 mm. per second) and double speed (50 mm. per second). The latter gives a "slow motion" tracing allowing easier differentiation of the various components of the complexes. Because of the rapid speed of the paper traveling at 50 mm. per second, quantitative comparison between these tracings and tracings taken at 25 mm. per second are not valid, since we attempted no calibration of our ballistocardiograph on high speed tracings. These

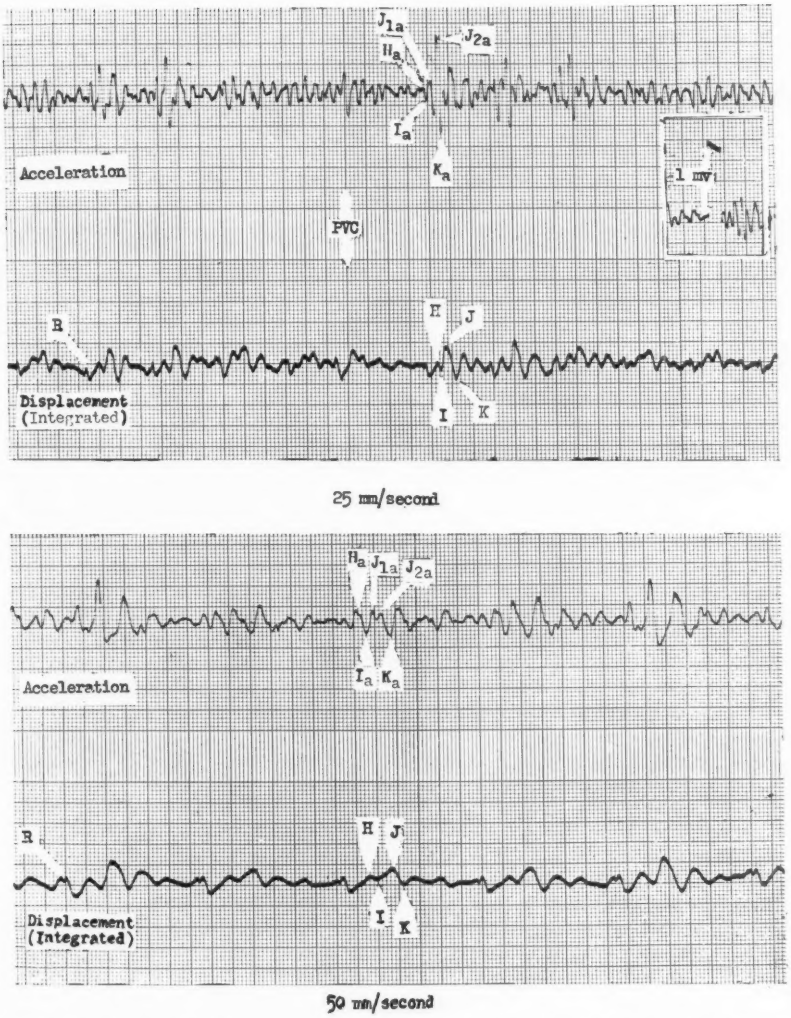

FIG. 6. Simultaneous displacement and acceleration tracings of A. H. Note that the 1 millivolt standardization is 16 mm. (as in all acceleration tracings illustrated) yet most of the J_a waves fail to represent more than 34.4×10^4 dynes and many are far less than that. Of interest is the definite biphasic component of the J_a wave following a compensatory pause after a premature ventricular contraction (labeled as J_{a_1} and J_{a_2} in the acceleration tracing). A notch is noted in the displacement J wave of the same origin, but the acceleration J_a wave clearly demonstrates the forces, as well as their direction, far more vividly. The high-speed tracing demonstrates notches of the I_a and J_a waves, not even suspected in the displacement I and J waves.

tracings are used merely to visualize more easily qualitative differences between velocity and acceleration tracings.

Figures 4 and 5 are tracings obtained from healthy males of ages 24 and 23, weighing 74 Kg. and 77 Kg., respectively, who show no evidence of any cardiovascular abnormality on physical examination or by electrocardiogram. They represent what we have found to be a representative range of amplitude and are considered to be normal ballistocardiograms. Figure 6 shows acceleration and displacement

ballistocardiograms in the case of a 51 year old white female weighing 55 Kg., six years after a myocardial infarction. Electrocardiograms revealed a left bundle branch block and an occasional premature ventricular contraction. She is on a full maintenance dose of digitalis and remains in borderline decompensation in spite of restricted activity and full digitalization. The high speed tracing (50 mm. per second) vividly demonstrates the notching of the J_a wave in acceleration as discussed above.

Summary and Conclusions

Acceleration is a valuable measurement in ballistocardiography. We have designed and constructed a portable, body-type, acceleration ballistocardiograph that is capable of directly sensing acceleration. It is easily constructed, free from complex electrical circuits, and yields consistent results. This accelerometer has a flat frequency response (without capacitance) from 0 to 3000 cycles per second and is linear well beyond the forces encountered in ballistocardiography.

The described accelerometer allows quantitative evaluation of ballistocardiograms, since it is readily calibrated by use of a simple pendulum, and once it has been calibrated on a pendulum its response can be standardized by use of the 1 millivolt standardization of the recording apparatus (electrocardiograph). Ballistocardiograms can be read quantitatively in terms of force allowing valid comparisons of tracings from one patient to another.

Examples of the clinical use of the acceleration ballistocardiograph have been presented revealing wave components in certain instances not seen in displacement ballistocardiograms.

Acknowledgment

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Sumario Español

La construcción de un acelerómetro linear para el uso en balistocardiografía se presenta incluyendo la relación entre aceleración, desplazamiento y velocidad. El elemento sensorio descrito es nuevo en el campo de la balistocardiografía y esta basado en un principio electroquímico. Una manera de calibrar el instrumento se describe, de esta manera permitiendo medidas cuantitativas de los varios componentes del balistocardiograma. Trazados de un individuo anormal y dos normales se ilustran para mostrar la relación entre desplazamiento y aceleración.

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CLINICAL PROGRESS

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Treatment of Bacterial Endocarditis

Dosage of Penicillin, Use of Other Antibiotics and Treatment of Patients with Negative Blood Cultures

By MAXWELL FINLAND, M.D.

THE STATUS of the therapy of subacute bacterial endocarditis, as of June 1950, was thoroughly and authoritatively reviewed by Bloomfield in his Lewis A. Conner Lecture of the American Heart Association which was published in this journal.[1] The same author has recently presented and discussed the problems of diagnosis and briefly touched on the prophylaxis of bacterial endocarditis in a recent issue.[2] The present discussion will, therefore, be limited chiefly to a consideration of certain topics of current interest. These will include: (1) the optimum method of administration of penicillin, (2) the use of antibiotics other than penicillin, and (3) the treatment of patients with negative blood cultures.

DOSAGE OF PENICILLIN

It is now generally agreed that penicillin, when properly used, is the antibiotic which by itself, or when used in proper combinations with other antibiotics, is responsible for all but a small proportion of the cures of cases of bacterial endocarditis. For an appreciation of the optimum method of administering penicillin in cases of bacterial endocarditis, one must consider the various factors entering into its curative action. These include: (a) the manner in which penicillin is absorbed and excreted, (b) the manner in which penicillin gets at the infecting organisms and eliminates them, and (c) the nature of the specific infectious lesion in this disease. Each of these features will be considered briefly.

Absorption and Excretion of Penicillin. Almost all of the penicillin that is given parenterally is accounted for by excretion through the kidney. The renal clearance of penicillin G in man approximates the total renal plasma flow and is independent both of the concentration of penicillin in the plasma and of the rate of urine flow.[3] Thus, the more rapidly penicillin gets into the blood, the higher and briefer is the peak level attained and the more rapidly will that level fall. That being the case, it is obvious that when repository preparations are used, the greater the delay in the absorption of the penicillin, the lower must be the peak level from any given dose and the more slowly will the blood level drop so that the lower levels will be sustained for longer periods.

Action of Penicillin. The experiments of Eagle and his associates[4] on the manner in which bacteria are cleared from a focus of infection should be studied in detail in order to be appreciated. For present purposes, however, it will suffice to note that from their experimental model, which was a streptococcal infection of the muscle of a mouse, they calculated that concentrations of up to 5 to 20 times those of the minimum inhibiting concentration for the organisms in vitro were required in order to achieve the maximum effective concentration at the site of infection. They also found that the aggregate time over which such concentra-

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tions are maintained at the focus of infection must be sufficient to eliminate all or almost all of the organisms. Moreover, the greater the number of organisms at the site of infection, the higher must be the concentration that is reached at that point and the longer must that concentration be sustained. Host mechanisms, which bring into play the circulating antibodies and leukocytes, may be effective in eliminating residuals of small numbers of certain organisms after the concentration of penicillin at the site of the infection has reached ineffective levels.

The Lesion in Bacterial Endocarditis. The important characteristics of the lesion as they relate to antibiotic therapy have now been well described.[5] These characteristics are: the absence of a blood supply in the tissue upon which the vegetation is implanted and the thick layers of dense fibrin, with some fibrous tissue and even calcium deposit which enclose the heavy concentrations of bacteria within the vegetations. Access to these organisms by elements within the blood, including penicillin, antibodies and leukocytes, is greatly impeded so that, on the one hand, it is difficult to attain the high concentrations of antibiotic needed at the site where the large numbers of organisms are congregated, and, on the other hand, there is little or no opportunity for the mediation of host mechanisms through the action of antibodies and leukocytes.

Weinstein, Daikos and Perrin[6] studied the diffusion of penicillin into subcutaneously implanted fibrin clots in rabbits. They found that after a large intramuscular dose, an equilibrium between the concentration of penicillin in the blood and within the clot may be reached after about two hours; by that time the blood level has already dropped to a fraction of its peak concentration. After that time, however, the concentration within the clot may be sustained at higher levels and for longer periods than in the plasma. These experiments, together with others of Eagle's which indicate that the action of penicillin on bacteria, both in vitro and in vivo, may persist for a limited period of time after the concentrations to which the organisms have been exposed has dropped to subinhibitory levels, serve to validate the effectiveness of "discontinuous" treatment, that is, the use of intermittent injections. They also suggest that perhaps the very high peaks of concentrations which are obtained by intermittent intramuscular injections of soluble preparations of penicillin are more desirable than the lower and more sustained concentrations achieved with equal or smaller total amounts of repository preparations, including the aqueous suspensions of procaine penicillin.

From these considerations it is the writer's present conviction that aqueous solutions of sodium or potassium penicillin are the dosage forms of choice for the treatment of bacterial endocarditis. The choice between these salts depends only on considerations of the status of the cardiac and renal function of the patient. Intermittent intramuscular injections at intervals of two to four hours are also considered to be the optimum method of administration.

The total dose of penicillin has been determined only empirically, and is one which will produce favorable effects in the great majority of cases. It is related only in a general way to the in vitro sensitivity of the organism, for that is only one of the factors entering into its effectiveness; the nature of the lesion, as already suggested, is probably of equal and sometimes of greater importance, and may be crucial. In general, daily doses of 1.2 to 3.0 million units per day (individual doses of 100,000 to 500,000 units) are adequate and probably offer a good margin of safety for the majority of cases which are due to *Streptococcus viridans*; most strains of these organisms are sensitive in vitro to concentrations ranging between 0.01 and 0.1 units per cubic milliliter. The need for larger doses is indicated when the organism is more resistant (the minimum inhibitory concentration for most strains of enterococci is usually in the range from 0.1 to 5.0 units per milliliter, but may be even higher), when bacteremia is not controlled, or when there is other evidence of persistence of active infection. Under such conditions, the dose should be increased rapidly to about 10 million units per day or more, and serious consideration should be given to the added use of other antibiotics, particularly streptomycin.

When the dose of penicillin required becomes

of such magnitude that the size of the individual intramuscular injection is difficult to tolerate,* it is best to resort to probenecid (Benemid), which, at present, is the best available agent to inhibit the renal excretion of penicillin. Doses of 2.0 Gm. per day (0.5 Gm. every six hours) given continuously, may permit reduction of the dose by one half or lengthening of the interval between doses; this interval, however, should never be more than six hours. An increase in the individual doses of probenecid from 0.5 to 0.75 or 1.0 Gm. will increase the retention and hence the blood levels of penicillin still further. When probenecid is used, it may also be possible to substitute some rapid intravenous injections for at least some of the intramuscular doses; this may have the advantage of producing still higher peaks of concentrations than are attainable by the intramuscular route, and at the same time reducing the local distress of the large injections.

In using probenecid during the treatment of cases of bacterial endocarditis it is important to bear in mind that in spite of the fact that this agent enhances the blood levels of para-aminosalicylic acid, its action may be neutralized by other salicylates; when probenecid is used, therefore, salicylates should not be given at the same time. Also, while probenecid serves to enhance the blood levels of penicillin and phenolsulfonphthalein, it does not have any effect on the excretion of streptomycin or of any of the broad-spectrum antibiotics. In patients with impaired renal function, probenecid is not usually needed, since relatively higher levels of penicillin are sustained from any given dose, as compared with those observed in patients with normal renal function.

Use of Antibiotics Other Than Penicillin

There are reports of cases in which almost every one of the antibiotics that have become commercially available has been used, either alone or in various combinations, for the treatment of cases of bacterial endocarditis. In some of the cases these antibiotics were used during clinical investigations of the activity of the new agents, but in most instances they were given either because of apparent failure to achieve a good response from penicillin or because the sensitivity of the organism in vitro was such as to suggest that a more favorable effect might be expected. The results of the use of these agents in cases of bacterial endocarditis are reviewed elsewhere[7]; they will be mentioned here only briefly, and the discussion of the different agents will be concerned primarily with those features of their use which pertain to their application in the treatment of cases of bacterial endocarditis.

Streptomycin. Next to penicillin, streptomycin has probably been used more than any other antibiotic for the treatment of cases of bacterial endocarditis. Its first and logical use was for the treatment of cases in which the causative organism was highly sensitive to streptomycin and relatively or markedly resistant to penicillin. However, the demonstration of an additive or synergistic effect in vitro on strains of streptococci from cases of subacute bacterial endocarditis when penicillin and streptomycin are used together, and the early favorable clinical reports on its use in patients with this disease led to the more frequent application of streptomycin, usually with penicillin, to all types of cases of bacterial endocarditis.

A brief survey of the results achieved in successive groups of cases in which streptomycin was used alone or with penicillin appears to indicate a steady improvement in the proportion of recoveries. Thus, cures were reported in only one-third of 39 cases with bacterial endocarditis collected by Keefer and Hewitt[8] during the early clinical trials of streptomycin conducted under the auspices of the National Research Council. By May 1949, Wallach and Pomerantz[9] were able to collect reports of 50 patients of whom 56 per cent recovered.

In 76 cases collected from other reports of patients who were treated subsequent to the appearance of these publications,[7] the cure rate

* Some of the pain from large intramuscular doses may be minimized by introducing 1 cc. of 2 per cent procaine hydrochloride into the syringe containing the penicillin solution *immediately* before each intramuscular injection.

was 75 per cent. This increase in the cure rate, however, was associated with the more frequent use of the streptomycin in combination with large doses of penicillin; there was also a decrease in the proportion of cases due to gram-negative bacilli or to organisms highly resistant to penicillin, and an increase in the proportion of cases due to nonhemolytic streptococci and other gram-positive organisms, in a large proportion of which penicillin alone might have proved effective if used in adequate doses.

In the last two series of cases there appeared to be a striking correlation between the sensitivity of the infecting organisms to streptomycin and the percentage of cures from treatment with that antibiotic; almost all of the patients whose organism was sensitive to less than 10 micrograms per milliliter recovered, whereas cures were infrequent among patients with more resistant strains. Moreover, contrary to what might have been expected, the development of resistance to streptomycin during treatment was only rarely encountered in the cases in which its use failed to bring about a cure. In most, though not all of these cases, the failure to develop resistance to streptomycin may have been due to the fact that this antibiotic was used in combination with penicillin. In vitro experiments in this laboratory have indicated that the development of resistance to various antibiotics, including penicillin and streptomycin, by staphylococci and some enterococci and nonhemolytic streptococci may be depressed or delayed, and sometimes prevented when the organisms are exposed to the combination of two antibiotics.[10] Personal observations have also indicated that streptomycin resistance may develop quite rapidly during even brief periods when this antibiotic is used alone for the treatment of cases of bacterial endocarditis.

These results would appear to warrant the conclusion that streptomycin is a highly useful agent in bacterial endocarditis when used alone for the treatment of infections with organisms that are highly sensitive to that antibiotic; it appears to be particularly useful in combination with penicillin for the treatment of infections due to organisms that are only slightly or moderately sensitive to the latter and to penicillin alone.

The dose of streptomycin most commonly used has been 2 Gm. a day, given either in two or four equally spaced intramuscular injections. It is usually possible to reduce this to 1 Gm. a day after two or three weeks when large doses of penicillin are also being employed. Larger doses of streptomycin have been used, but it is important to bear in mind that very high and toxic levels may be obtained in patients who have impaired renal function; in such patients, therefore, it should be possible to reduce the dose and thus avoid the early appearance of severe neurotoxicity from the streptomycin.

There is no sound basis for the prevailing trend toward use of dihydrostreptomycin instead of streptomycin.[11] Both forms produce damage to the eighth nerve when they are used in moderate or large doses continuously over long periods; however, with dihydrostreptomycin, loss of hearing predominates and occurs in about the same frequency as do the vestibular symptoms from the use of streptomycin, which only rarely produces deafness. Sensitization reactions are somewhat less frequent with dihydrostreptomycin, but when sensitization occurs with the use of streptomycin, a change to dihydrostreptomycin can generally be made without further reaction.

There is some recent evidence that the toxicity of these agents on the eighth nerve may be markedly reduced and possibly eliminated by using the two forms in a 1 to 1 ratio. However, until this is confirmed in a large number of cases, it would appear safer to use the one, and then changed to the other at the first evidence of the appearance of toxicity. Because deafness from dihydrostreptomycin is often insidious in appearance, may not be made out until after the treatment is stopped and is usually irreversible, whereas the evidence of vestibular damage can be detected early, at a stage when it is still reversible, it would appear preferable to start treatment with streptomycin and then to change to dihydrostreptomycin if toxicity develops.

Bacitracin. This agent is active only against gram-positive organisms and its possible use-

fulness in bacterial endocarditis is suggested by the fact that in vitro an additive or synergistic effect with penicillin has been demonstrated against some strains of streptococci obtained from cases of this disease. The major drawback to the use of bacitracin has been its nephrotoxicity which is apparently intimately related to its antibacterial action. However, when used in intramuscular doses of 100,000 units per day or less, only minor and transient effects on renal function and on the urinary findings are noted. The daily dose is usually given in three or four equally spaced intramuscular injections. Local irritation at the site of the intramuscular injections is frequently encountered; this may be reduced by diluting the bacitracin in 1 or 2 per cent procaine.

The results in the reported cases that are available for evaluation have been almost uniformly favorable with the doses mentioned, given in combination with large doses of penicillin. There was one favorable result from the use of bactracin alone, and the only failure was recorded in a patient who was treated with increasing doses of bacitracin for pneumococcal pneumonia complicated by meningitis and endocarditis. In the latter case evidence of renal damage attributable to bacitracin was found at autopsy, but doses up to 400,000 units per day had been given.

From the meager data that are available, it may be stated that bacitracin can be recommended as an agent which merits further trials under controlled conditions and in conjunction with penicillin in cases of bacterial endocarditis due to gram-positive organisms, particularly those which are not highly sensitive to the latter antibiotic alone.

Broad-Spectrum Antibiotics. The three antibiotics commonly included in this category are chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and chloramphenicol (Chloromycetin). Each of these antibiotics has been used for the treatment of cases of bacterial endocarditis; they were used only rarely alone, but more often in various combinations involving one or more of them with penicillin, or streptomycin, or both, and in an occasional patient a sulfonamide was thrown in for good measure. An analysis of reports collected from the literature in more than 67 cases of bacterial endocarditis treated with Aureomycin, 27 with Terramycin and 13 with chloramphenicol is given elsewhere.[7] Between 32 and 44 per cent of the patients were cured during treatment with one or another of these agents and in most, though not all, of the cured patients other antibiotics were given at the same time. The results with Aureomycin appeared to be slightly, though not significantly superior to those obtained with the other two agents, but comparisons in such small numbers hardly seem warranted.

In most of the patients, these antibiotics were given only by mouth, but the intravenous route was used in some of the patients who received Aureomycin, especially at the beginning of therapy or as a supplement to oral treatment later during times when untoward gastrointestinal symptoms were encountered. The most frequent oral dose of each of these agents was between 2 and 4 Gm. per day, given in four to eight doses. The usual intravenous dose was 500 mg. given as an infusion in saline twice a day, but only one daily injection was generally used to supplement oral therapy.

From the review of these cases it would appear that some patients may be favorably affected and even cured with one or another of these broad-spectrum antibiotics. The results with these agents, however, are far less impressive than those with penicillin alone and particularly with the combination of penicillin and streptomycin. However, some of the cures, particularly as a result of Aureomycin, were obtained in patients in whom penicillin alone or in combination with streptomycin had apparently failed. With each of these agents highly favorable clinical effects and failure to obtain positive blood cultures were noted in some patients during their administration, but clinical and bacteriologic relapses occurred either during the continued therapy or promptly after that antibiotic was stopped. These effects are usually attributed to the mode of action of the broad-spectrum antibiotic which is considered to be bacteriostatic rather than bactericidal. In some of the cases of failures from each of these three antibotics cures were subsequently obtained by the use

of other antibiotics, singly or in various combinations (some of which included the broad-spectrum antibiotic which alone had failed) but most frequently with large doses of penicillin combined with streptomycin.

Considerable interest has been focused recently on the problem of synergism and antagonism which may of course come into play in the treatment of cases of bacterial endocarditis when multiple antibiotics are employed. Some aspects of this subject have recently been reviewed by Jawetz and Gunnison.[12] Judging from experimental data, antagonistic action between antibiotics may be expected in certain cases from the use of the broad-spectrum antibiotics in combination with penicillin or streptomycin. However, there is as yet no proof that such an effect has been responsible for any significant number of failures in bacterial endocarditis, although the findings in some cases may be open to such interpretations.

The only recommendation that seems warranted from the results thus far obtained is the obvious one that the sensitivity of the infecting organisms in cases of bacterial endocarditis should be tested with all of the antibiotics which might possibly prove useful and that tests with pairs of these antibiotics should also be included. The use of the broad-spectrum antibiotics would then be reserved only for patients in whom penicillin alone or in combination with streptomycin or bacitracin has failed, or where such failure might be predicted from the resistance of the organism to these agents in vitro, or when the use of these agents is not possible because of marked hypersensitivity. The broad-spectrum antibiotics are not to be recommended for the initial therapy of doubtful cases, or when treatment is undertaken before the sensitivity of the organism is known, or in patients with negative blood cultures.

Erythromycin (Ilotycin) and Carbomycin (Magnamycin). The use of these new antibiotics, each of which has an antibacterial spectrum similar to that of penicillin, has been reported in only a few patients with bacterial endocarditis.[7] However, in only one of the cases reported at the time of this writing was treatment with erythromycin successful, whereas similar treatment failed in six other patients and four of these failures were associated with the rapid development of resistance to erythromycin in the infecting organism during treatment with that agent. Carbomycin failed to yield a single cure in the six patients with bacterial endocarditis in whom it was used.

Maximum tolerated doses were used orally in all of these patients, and in some of those treated with carbomycin they were supplemented with intravenous injections of the same agent. In the majority of the patients in whom failures were reported from these two antibiotics, cures were subsequently obtained by the use of large doses of penicillin, either alone or together with streptomycin.

In vitro experiments in this laboratory have shown that when certain bacteria are exposed to the combination of erythromycin with either penicillin or streptomycin, the development of resistance to each of these antibiotics may be delayed or depressed. Whether or not the use of such combinations in the treatment of bacterial endocarditis due to susceptible organisms will prove more successful than the use of these new antibiotics alone remains to be determined. At present the use of these antibiotics in the treatment of bacterial endocarditis cannot be recommended, except where carefully controlled studies could be made.

Treatment of Patients with Negative Blood Cultures

Patients with bacterial endocarditis in whom one fails to obtain positive blood cultures present a special and difficult problem. The importance of these cases may be judged from the fact that in some of the reported series, the mortality is twice as high, or even greater, among those patients as in those in whom positive blood cultures are obtained. Among the reasons offered for this difference in mortality are: (1) delay in treatment, (2) erroneous diagnosis, (3) inadequate or improper treatment; all of these are due to the fact that a positive blood culture is not available as a guide.[13] It may also be suggested that in such cases a deep focus of infection well protected

by fibrin and fibrous tissue and perhaps by calcium deposits may be responsible for both the failure to obtain a positive blood culture and for the poor therapeutic results. If the latter explanation is valid, one should expect improvement in the results if such patients are treated with massive doses of penicillin, perhaps in combination with streptomycin. The good results reported by Loewe and Eiber[14] in a group of such cases may be cited in support of this view. On the other hand, the poor results have usually been correlated with the presence of severe complications, particularly congestive heart failure and serious or extensive embolization.

In order to reduce to a minimum the number of failures in these cases, Friedberg[13] has suggested that insistence on obtaining a positive blood culture be eliminated from the criteria for the diagnosis of bacterial endocarditis for the purpose of initiating antibiotic therapy. This is a reasonable suggestion, but, if adopted, one should also insist on certain other steps: (a) some definitive clinical criteria for the diagnosis of bacterial endocarditis; (b) exclusion of other important diseases which could account for the clinical findings; (c) a delay of at least two days before treatment is initiated, during which period blood cultures should be made on several occasions; (d) the media used for the cultures should include those which permit the growth of anaerobic bacteria, fungi and certain fastidious organisms like Brucella, Hemophilus and Neisseria, and the cultures should not be discarded until they have been incubated and examined over a period of three weeks; (e) cultures of aspirated bone marrow may also be useful particularly in patients who have recently been treated with antibiotics.[15] A delay of more than 48 hours under the above conditions is probably of very little if any advantage.[16]

For the initial treatment of these cases before the results of a blood culture are obtained a regimen comparable to that which is used in the treatment of subacute bacterial endocarditis due to a relatively resistant organism is adopted. This includes massive doses of penicillin plus streptomycin. One may begin with a dose of 1.2 to 3.0 million units per day of penicillin alone, but this should be increased within a week to at least 10 million units a day and 2 Gm. of streptomycin daily should also be given if clinical improvement does not result. Should any of the cultures obtained before treatment subsequently turn positive, the organism should be tested for sensitivity, and any treatment that has been undertaken could then be changed to accord with the results of these tests if the response of the patient by that time appears to be inadequate or poor.

The use of corticotropin (ACTH) or cortisone in such cases has been suggested, but is not to be recommended, except as an investigative procedure carried out with the greatest of care and under strictly controlled conditions. The depression of resistance to infection during administration of these hormones has now been demonstrated in a wide variety of experimental and clinical infections. Even in cases with active acute rheumatic fever, the use of corticotropin and cortisone involves a definite risk of bacterial infection developing on valves not previously infected, or of aggravating a bacterial endocarditis that is already present, and possibly also of reducing the efficacy of antibacterial therapy.[17]

Summary and Conclusions

The dosage of penicillin has been discussed on the basis of the known properties of that antibiotic and the characteristics of the lesion in the patients with bacterial endocarditis. Reasons have been given for the choice of large and frequent intramuscular doses of the aqueous soluble salts of penicillin G, supplemented in certain cases by the oral use of probenecid (Benemid) as the optimum method for using penicillin in this disease.

The status of the use of antibiotics other than penicillin in the treatment of cases of bacterial endocarditis has also been reviewed. Streptomycin appears to be firmly established as a highly valuable agent in this disease, particularly when used in conjunction with large doses of penicillin. Favorable reports of the use of bacitracin in doses of 100,000 units per day in combination with large doses of penicillin indicate that further trials of this

antibiotic are warranted. The broad-spectrum antibiotics particularly chlortetracycline (Aureomycin) have proved to be life-saving in individual cases; the over-all results from the use of these agents, however, have not been nearly so impressive as from penicillin and streptomycin. Erythromycin and carbomycin have thus far proved ineffective.

The problem presented by the patient with a clinical diagnosis of bacterial endocarditis but with negative blood cultures is also discussed. Intensive clinical and bacteriologic study during a period of about 48 hours, followed by treatment with large doses of penicillin in combination with streptomycin is suggested for the management of these cases, with less delay only when they are particularly severe and of long standing, or already show evidence of cardiac failure or extensive or significant embolic phenomena.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Farmer, E. D.: Streptococci of the Mouth and Their Relationship to Subacute Bacterial Endocarditis. Proc. Roy. Soc. Med. **46**: 201 (Mar.), 1953.

In this paper it has been shown that 37 per cent of the streptococci present in the mouths of 25 apparently normal patients could be classified as members of Lancefield serologic groups. Many of the streptococci reported as being isolated from the blood of patients with subacute bacterial endocarditis are culturally, biochemically, and serologically similar to those found in the mouths of almost half of the normal patients investigated. Bacteria enter the blood stream during the extraction of teeth in about 40 per cent of cases, but in only about 10 per cent of cases of subacute bacterial endocarditis has the onset of symptoms been associated with recent dental extractions. There has frequently been reported a similarity between the organisms in the blood and the organisms present in the mouths of patients with subacute bacterial endocarditis, but this similarity is usually confined to the type of hemolysis produced on blood agar, or to the results of certain cultural and biochemical tests. If the mouth were the original source of the strain causing the heart lesion, it would be expected that serologically identical strains could be found in both the blood and the mouth of the patient concerned. It may be that by using serologic methods further, work will reveal identical strains from both sources, but as yet no such reports have been noted.

It is concluded that although it has not been established that the mouth is a focus of infection in the etiology of subacute bacterial endocarditis, the finding in the mouths of normal patients of bacteria that are serologically similar to those isolated from the blood of many cases of subacute bacterial endocarditis, suggests that precautions should be taken to protect the patient with a susceptible heart lesion from the possible consequences of bacteremia during dental operations.

BERNSTEIN

BLOOD COAGULATION

Quick, A. J., Murat, L. G., Hussey, C. V., and Burgess, G. F.: The Prothrombin in the Newborn. Surg., Gynec. & Obst. **95**: 671 (Dec.), 1952.

Studies of prothrombin activity were made on maternal blood, umbilical cord blood, and the infant's blood 10 minutes after delivery. Two groups were used; in one, the mothers received vitamin K prior to parturition, and in the other, they did not.

The one stage prothrombin test was used to determine the level of free prothrombin. The two stage prothrombin test was added to measure the total prothrombin which is the free prothrombin plus the inactive prothrombin (prothrombinogen).

The results indicated that there was a consistent prolongation of the prothrombin times of both the infant's blood and the cord blood when extra vitamin K was not administered before delivery. This was even present to a lesser degree in the maternal blood.

When vitamin K was given to the mother prepartum, the prothrombin times of the maternal blood, the cord blood, and the infant's blood were normal.

The two-stage test indicated that the maternal blood had a normal level of free prothrombin and prothrombinogen. In the infant, no prothrombinogen could be found. It would appear that in the newborn all of the prothrombin is in the free state and thus the total prothrombin is only 25 per cent of that of the adult. The administration of vitamin K did not alter this. The infant is probably unable to form

prothrombinogen. At the age of 1 year, however, a normal level of total prothrombin exists.

FROBESE

Van Buskirk, W. C.: The Effect of Intravenous Injection of Emulsified Vitamin K_1 on the Hypoprothrombinemia Induced by Tromexan. New England J. Med. **248:** 57 (Jan. 8), 1953.

The effect of emulsified vitamin K_1 on a low plasma prothrombin level resulting from the administration of Tromexan was studied in 10 patients. The dosage of the medication was 5 mg. per kilogram of body weight given intravenously.

In all subjects there was a demonstrable elevation of prothrombin activity beyond the dangerous range three hours after the drug was given. No untoward responses were noted. It was therefore concluded that the antagonistic action of emulsified vitamin K_1 on the hypoprothrombinemia produced by Tromexan was approximately the same as that on the hypoprothrombinemia which follows the use of Dicumarol and phenylindandione.

ABRAMSON

Avellaneda, M., Castro, C. M., and Stritzler, G.: A New Anticoagulant Tromexan. Its Action in the Normal and in Various Pathologic Conditions, and its Interference with Other Medications. Cardiologia **22:** 321 (Fasc. 6), 1953.

The authors report the methods of application, and some characteristics of Tromexan which were used in 34 patients with various cardiovascular affections. The optimal initial dose is 1200 mg. followed after 12 hours by 300 mg.; the maintenance dose is 150 mg. every 12 hours. The prothrombin time begins to increase 16 hours after the beginning of treatment, is considerably prolonged after 24 hours and returns to normal after 36 to 48 hours. A proper maintenance of low prothrombin levels is easier to accomplish in hospitalized than in ambulatory patients. In no case was there a tendency to bleeding or toxic phenomena. Sodium salicylate enhances the action of Tromexan; mercurial diuretics and α-tocopherol have an uncertain, and aminophylline no effect, on the action of the drug.

PICK

Beaumont, J. L., Chevalier, H., and Lenègre, J.: Studies on Spontaneous Variations in Blood Coagulability Immediately Following Myocardial Infarction. Am. Heart J. **45:** 756 (May), 1953.

A study of the coagulability of the blood was made in 70 cases of myocardial infarction untreated by anticoagulants. The initial measurements of blood coagulability were made: within 24 hours of the attack in 12 cases; within 48 hours of the attack in 13 cases; within 4 days of the attack in 32 cases; and between the fourth and ninth day in 13 cases. Further tests were made on all every two days at first and then later at more widely spaced intervals. The tests used were: (1) heparin tolerance test (in vitro), (2) plasma prothrombin; and (3) plasma fibrinogen.

Three phases were delineated: (a) a period of hypercoagulability which occupied the first 24 to 48 hours; (b) a period of spontaneous, hypocoagulability from the second to third to eighth to fifteenth day, usually lasting about seven days; (c) a period of late hypercoagulability, variable in degree, starting on about the eighth or tenth day and lasting usually a few weeks but possibly several months.

The demonstration of these spontaneous fluctuations of coagulability indicate that frequent studies of blood coagulability are essential and that prothrombin time by itself is not enough, but that heparin tolerance in vitro must always be made at the same time.

Application of these principles to 71 patients with myocardial infarction treated with anticoagulants resulted in an over-all mortality of 9.8 per cent and a 2.8 per cent incidence of thromboembolic complications. The bleeding incidence was 12 per cent.

RINZLER

Weiner, M., Simson, G., Burns, J. J., Steele, J. M., and Brodie, B. R.: The Control of Prothrombin Activity with Tromexan Therapy. Am. J. Med. **14:** 689 (June), 1953.

The authors find it more difficult to achieve clinical control of reduced prothrombin activity with Tromexan than with Dicumarol. Wide individual variations in response to Tromexan make it difficult to determine that initial dose which will produce an adequate prothrombin response within 24 hours. Maintenance doses varied from 150 to over 1,000 mg. daily. Sudden unpredictable changes in prothrombin time with the patient receiving regular daily doses of Tromexan are frequent. The safe administration of Tromexan requires at least daily prothrombin time estimations. In most instances the prothrombin time returns rapidly toward normal after Tromexan is discontinued.

HARRIS

Cosgriff, S. W.: Chronic Anticoagulant Therapy in Recurrent Embolism of Cardiac Origin. Ann. Int. Med. **38:** 278 (Feb.), 1953.

In an attempt to prevent or to reduce the incidence of recurrent embolism, protracted anticoagulant therapy on an ambulatory basis has been carried out in 35 patient-courses among 28 patients with mitral stenosis and auricular fibrillation who had already experienced one or more emboli of intracardiac origin. One hundred and three emboli had occurred during 275 patient-months prior to such treatment; 13 emboli have occurred during 625 patient-months under therapy. Furthermore, approximately three fourths of the 17 patients in whom long-term use of the anticoagulant has been dis-

continued have suffered another embolism after cessation of Dicumarol treatment, that is, there were 14 embolic episodes in 239 patient-months. Thus, at the present stage of our knowledge it appears that once an individual has demonstrated a propensity to recurrent embolism for which prophylactic anticoagulant treatment has been administered, this therapy should be continued for an indefinite period. Chronic ambulatory administration of anticoagulants is practical and safe provided there is careful professional supervision and reliable laboratory control. This group of patients has received Dicumarol for a combined total of 625 patient-months, with only one instance of major hemorrhage.

WENDKOS

CONGENITAL ANOMALIES

Soulié, P., Carlotti, J., Voci, G., and Joly, F.: The Physiopathology of Eisenmenger's Complex. Arch. mal. coeur **46**: 481 (June), 1953.

The authors report detailed hemodynamic studies in 12 cases, 6 to 28 years old, of Eisenmenger's complex. At birth the principal factor determining the pathophysiology of this malformation is the overriding aorta. At this stage, the pressures in both ventricles, and in the aorta and pulmonary artery are equal. The presence of a high pressure in the pulmonary arterial bed causes the development of an increased pulmonary vascular resistance which is necessary to protect the pulmonary capillary system from hypertension and to maintain a circulatory equilibrium compatible with life.

The changing relationship of pulmonary and peripheral vascular resistance in the course of this development permits the distinction, from the hemodynamic standpoint, of two principal stages of the condition. In the first, acyanotic period the intracardiac shunt is directed entirely from left to right. The pulmonary resistance is lower and the pulmonary flow higher than respective values of the systemic circulation. The second, cyanotic period develops when the pulmonary arterial resistance exceeds the peripheral resistance. The desaturation of the peripheral blood is due entirely to the intracardiac shunt as evidenced by the normal oxygen content of pulmonary venous blood found in instances of Eisenmenger's complex associated with atrial septal defects. Usually there is only a right-to-left shunt but occasionally the shunt may be bidirectional—the pulmonary flow exceeding the systemic flow. These variants of the hemodynamics depend on the degree of the transposition (overriding) of the aorta. They account for acyanotic instances of Eisenmenger's complex, and illustrate the difficulty of differentiating, from the hemodynamic standpoint, Eisenmenger's complex from the syndrome of interventricular communication associated with pulmonary hypertension and a normally placed aortic root.

PICK

Geraci, J. E., and Burchell, H. B.: Congenital Pulmonary Stenosis With Intact Ventricular Septum in Persons More Than 50 Years of Age. Proc. Staff Meet., Mayo Clin. **28**: 346 (June), 1953.

The clinical and necropsy findings are presented in two cases of congenital pulmonary valvular stenosis with intact ventricular septum. In the first of these two cases the atrial septum was anatomically sealed. In the second case the foramen ovale was probe patent, that is, under circumstances of normal pressure relationships between the two atria, no outflow through the foramen ovale would have been expected. In the event that the right atrial pressures should have exceeded the left, a small shunt from right to left could have occurred through the foramen ovale. These two cases illustrate two of the common modes of death in pulmonary valvular stenosis with intact ventricular septum, namely, congestive cardiac failure, as observed in the first case, and bacterial endocarditis, as observed in the second case.

SIMON

Robbins, L. L., and Wyman, S. M.: Coarctation of the Thoracic Aorta. Signs Demonstrable by Conventional Roentgenography. New England J. Med. **248**: 747 (April 30), 1953.

The report is based upon the study of a group of 31 patients in 20 of whom surgical or pathologic proof of coarctation of the aorta had been obtained. Opaque contrast studies were done in 14 cases and in 7 others the clinical and conventional roentgenographic evidence was considered conclusive. Notching of the ribs was absent or questionable in eight cases. The earliest age at which it appeared in this series was 6 years; 12 years is said to be the usual age at which it appears. In five cases there were scalloped indentations in the anterior margins of the lungs suggesting multiple soft-tissue masses due to dilated, tortuous internal mammary arteries. Other indirect signs of coarctation include absence of the expected prominence of the aortic knob, absence of the usual aortic-arch impression upon the barium-filled esophagus, increased prominence of the ascending aorta with increased amplitude of pulsations due to increased blood pressure, hypertrophy and enlargement of the left ventricle, and widening of the left superior mediastinum due to dilatation of the left subclavian artery. There is often an exaggerated convexity of the proximal descending aorta due to dilatation of the aorta below the coarctation. The "poststenotic bulge" of the aorta displaces the barium-filled esophagus anteriorly and to the right.

The primary finding in coarctation of the aorta is narrowing which can be visualized most accurately by angiography. The corresponding narrowing of the outside of the vessel appears on plain films as an indentation of the left lateral and posterior aspects of the proximal descending aorta outlined by contrast with the air-containing lung and with the barium-filled esophagus. Where the outer wall of the aorta is in contact with the left lung, a definite indentation is visible in the posteroanterior, left anterior oblique or lateral projection. The barium-filled esophagus exhibits a corresponding protrusion indicating the other side of the coarctation. This protrusion is said to be the valley between the impressions produced by the wider portions of the aorta above and below the point of narrowing.

Because it is a study of living, gross anatomy, angiography is said to furnish an even more accurate diagnosis than a postmortem examination. Its diagnostic value may exceed thoracotomy since it demonstrates areas which may not be accessible to surgical exploration. Contrast studies furnish the surgeon with information regarding the length and location of the coarctation, the lumen of the vessel, the extent of the collateral circulation, and the presence of coexisting congenital anomalies.

ROSENBAUM

Marder, S. N., Seaman, W. B., and Wilson, H. M.: The Pulmonary Circulation in the Diagnosis of Congenital Heart Disease. J. Thoracic Surg. **25:** 305 (Mar.), 1953.

A comparison was made of the data on the pulmonary circulation obtained with conventional roentgenographic examinations, angiocardiography, cardiac catheterization, operative findings, and a study of autopsy material. It was found that the conventional roentgenograms, together with a competent clinical history, physical examination and unipolar electrocardiograms, provided all the essential information in the majority of patients. The more expensive and hazardous diagnostic procedures, such as cardiac catheterization and angiocardiography, were believed to be indicated only for a few of the rarer and more complicated congenital abnormalities of the heart.

ABRAMSON

Wilson, J. G., Lyon, R. A., and Terry, R.: Prenatal Closure of the Interatrial Foramen. Am. J. Dis. Child. **85:** 285 (Mar.), 1953.

Prenatal closure of the interatrial foramen causes developmental distortions of the heart which are not compatible with postnatal life for more than a few hours or days. The absence of such a foramen during fetal life deprives the left atrium and left ventricle of all but the relatively small amount of blood brought by the pulmonary veins. This is an insufficient amount to bring about normal dilation and muscular development of the left-sided chambers, which therefore remain more or less hypoplastic. Such hypoplasia may be tolerated during fetal life, but the increased amounts of blood which shortly after birth begins to flow through the lungs and into the left atrium and ventricle cannot be accommodated by these underdeveloped chambers. Pulmonary venous congestion, accompanied by cyanosis and dyspnea, is the result.

Two cases of prenatal closure of the interatrial foramen have been described. These together with 15 cases found in the medical literature have been compared in regard to clinical manifestations of the patients and the anatomic features of their hearts. The possible manner in which the condition originated in embryonic life has been discussed briefly.

BERNSTEIN

CONGESTIVE HEART FAILURE

Perlia, A., Froment, R., and Lenègre, J.: Cardiac Failure in Young Subjects due to Dense and Diffuse Myocardial Sclerosis of Tuberculous, Uncertain or Unknown Etiology. Cardiologia **22:** 257 and 333 (Fasc. 5 and 6), 1953.

The authors describe a group of 30 patients (six personal observations), less than 40 years old, who at autopsy showed severe myocardial fibrosis without any evidence of coronary disease. From the clinical standpoint the condition presents itself with a picture of rapidly progressing heart failure affecting predominantly the left ventricle. A common associated finding is peripheral embolization originating from ventricular thrombi. The average duration of life from the onset of symptoms is two years.

The anatomic lesions in the heart resemble macroscopically the scarring seen following myocardial infarction, but the alterations are more extensive and more diffuse. Histologically all stages between simple inflammatory edema and dense fibrosis can be present. As a rule, the arterioles are not affected. In six of the cases concomitant tuberculous lesions were found in the lungs and in the mediastinum. Although there was no evidence for tuberculosis in the myocardial lesions, for these six instances the authors consider the possibility of a "subacute tuberculous myocarditis" as described by Josserand and Gallavardin. In the remaining cases the etiology was obscure. Statistically this syndrome represents only a small proportion (0.25 to 0.4 per cent) among cases dying from congestive heart failure in general.

PICK

Wolfe, L. S., and Geiger, A. J.: Urticaria Due to Drugs of the Digitalis Series. New England J. Med. **248:** 148 (Jan. 22), 1953.

A woman aged 82 years who developed urticaria after each of a large series of drugs in the digitalis group is described. The drugs studied included digitalis whole leaf, digitoxin, Digoxin, Digilanid,

lanatoside C and Urginin (squill glycoside). At least a three-week interval was allowed between the various drugs. When digitalization was induced rapidly prompt diuresis and symptomatic improvement occurred without immediate urticaria. However, as a maintenance dosage was continued or if the original digitalization was spread over one week, urticaria invariably appeared. The intensity of eruption was the same with each drug. Antihistaminic medication allayed the itching but did not abolish the lesions. The urticaria cleared when the drugs were stopped—the speed of clearing corresponding to the generally accepted duration of action of each of the drugs. When digitoxin was continued in the hope that desensitization would result, frequency, urgency, prolapse of the urethral meatus and a dusky edema of the bladder appeared forcing discontinuance of the drug. Eosinophilia did not accompany the urticaria nor did scratch or patch tests prove positive. The allergic response was attributed to the cyclopentenophenanthrene nucleus, common to all of the cardiotonic glycosides studied.

ROSENBAUM

Love, D. E., and Levine, S. A.: Mitral Stenosis with Long-Lasting Congestive Heart Failure or Auricular Fibrillation. New England J. Med. **247:** 917 (Dec. 11), 1952.

A comparative analysis of the average duration of life after onset of congestive heart failure or auricular fibrillation in cases of mitral stenosis, observed at the Peter Bent Brigham Hospital in the period from 1913 to 1926 as contrasted with the period from 1926 to 1946, disclosed an average survival of two and one-fourth years in the former and three and three-fourths years for the latter group—a gain of a year and a half. It is inferred from this that the treatment of heart failure has improved. In a series of 510 patients with mitral stenosis, 8 per cent survived nine or more years after the onset of fibrillation or congestive failure. Of those observed more recently it appeared that 10 to 13 per cent of all cases of mitral stenosis fell into the prolonged survival classification.

There were 65 patients, who survived nine or more years after the onset of congestive failure or permanent auricular fibrillation, available for study. The average interval from the onset of rheumatic fever to death was 36 years. The average interval from the onset of rheumatic fever to the onset of congestive failure or auricular fibrillation was 23 and 25 years, respectively. Of the 41 patients who died, 29 succumbed as a result of heart failure, 7 died of systemic or massive pulmonary emboli, 2 died as a result of lobar pneumonia and quinidine caused the death of two others. Bacterial endocarditis was not the cause of death in any case. One patient is described who recently underwent mitral valvuloplasty despite the fact that she had permanent auricular fibrillation for 26 years. There was a great preponderance of women in this special series of patients. Fifty per cent of the group were considered hypertensive. Although 25 per cent of the patients had symptoms suggesting angina pectoris, it is mentioned that the angina-like pain of pulmonary arterial hypertension may have accounted for this symptom in some of these patients. Tricuspid stenosis was present in one-fourth of this series of cases, suggesting that this valvular lesion was a factor in the long survival, since it occurs in only a tenth of all cases of rheumatic heart disease.

It is pointed out that in judging the indications for surgery in patients with mitral stenosis and evaluating the duration of life after operation, data such as these concerning long survival deserve consideration.

ROSENBAUM

CORONARY ARTERY DISEASE

Phares, W. S., Edwards, E., and Burchell, H. B.: Cardiac Aneurysms: Clinicopathologic Studies. Proc. Staff Meet., Mayo Clin. **28:** 264 (May), 1953.

A review of 40 cases of cardiac aneurysm disclosed a predominantly anterior and apical distribution of the lesions, with a great majority of specimens demonstrating severe atherosclerosis of the anterior descending branch of the left coronary artery. Left ventricular thrombi were found in 27 instances, and systemic arterial occlusion or insufficiency occurred in connection with six of these. There were no instances of rupture of the aneurysm. Congestive heart failure was the most common complication, and this along with coronary insufficiency accounted for most of the deaths.

The data do not permit definite conclusions regarding the significance of inadequate early therapy of myocardial infarction as a precipitating factor of cardiac aneurysm, but they did suggest that continued normal activity during acute myocardial infarction might have been an important predisposing factor. Careful roentgenologic examination of patients who have had previous myocardial infarction and who may have a persistent elevation of the S-T segment in the appropriate electrocardiographic leads apparently offers the best clue to antemortem diagnosis of this condition.

SIMON

Spain, D. M., Bradess, V. A., and Huss, G.: Observations on Atherosclerosis of the Coronary Arteries in Males Under the Age of 46: A Necropsy Study with Special Reference to Somatotypes. Ann. Int. Med. **38:** 254 (Feb.), 1953.

The data in 111 consecutive necropsies in white males under the age of 46 who died suddenly are reviewed with particular reference to the occurrence of coronary disease in relation to the various basic somatotypes. Thirty-eight of these males had died suddenly and unexpectedly from coronary artery

disease, while the remaining 73 subjects died suddenly from unexpected, violent causes. The major anatomic finding in those dying from coronary artery disease was advanced sclerotic narrowing of the coronary arteries with varying degrees of obstruction. Unusual findings were thrombi or myocardial infarcts in these cases. This low incidence of myocardial infarction is attributed to the brief interval of time between the episode of coronary insufficiency and death. Analysis of the findings in the 73 patients who had died from violence indicated that advanced coronary sclerosis was present in 12 of these cases and that of this number, 10 were mesomorphs and 2 were mixed somatotypes. Advanced coronary sclerosis was not observed in the pure ectomorphs or endomorphs in those dying suddenly from violence. This observation is particularly significant since the various body types in those dying from noncardiac causes were distributed as follows: mesomorphs 30, ectomorphs 24, endomorphs 7, mixed type 12. The observation that one-half of apparently healthy young males between the ages of 36 and 46, when dying suddenly from violence, were also victims of anatomically significant coronary atherosclerosis has an important bearing on previously published studies employing individuals within this age range as normal controls merely on the basis of absence of symptoms and absence of abnormal physical or laboratory findings. In the present series, no relationship was noted between obesity and coronary atherosclerosis. Also there were no apparent differences in heart size in those with coronary artery disease as compared with those with relatively uninvolved coronary arteries. No anatomic differences in the pattern of the coronary circulation were noted among the various somatotypes, nor were any noted between those with and those without coronary artery disease. An analysis of the various types of physique in the 38 consecutive necropsied individuals who died from the complications of coronary artery disease indicated that the mesomorphic group predominated in these cases. The proportion of dominant mesomorphs who died suddenly from coronary artery disease is undoubtedly higher than the percentage of mesomorphs in the general population. This fact should be borne in mind in selecting individuals for control studies in connection with the matter of coronary atherosclerosis, particularly since many of these individuals who died suddenly from the complications of their coronary artery disease had no preceding indications of the existence of coronary atherosclerosis.

WENDKOS

Fink, T. R., d'Angio, C. J., and Biloon, S.: Clinical Study of Shock Following Myocardial Infarction. J.A.M.A. **151**: 1163 (April 4), 1953.

Clinical observations on 15 patients with shock following acute myocardial infarction are described. The patients are divided into two groups. Group I were those with low venous pressure who responded to the use of phenylephrine (Neo-Synephrine) hydrochloride by a rise in both venous and arterial pressures. These patients resemble those with the shock state following trauma. Group II were those with high venous pressure who responded to the administration of lanatoside C by a rise in arterial pressure and in some cases by a fall in venous pressure. It was felt that these patients were in severe heart failure and the use of intravenous plasma, intra-arterial transfusion, or phenylephrine hydrochloride in the treatment of this syndrome was clearly contraindicated. Mortality in all cases was very high. One patient of 5 in the low venous pressure group survived over a month's time, and of the 10 patients in the high venous pressure group only 2 recovered.

KITCHELL

Dack, S., and Gorelik, A. N.: Cardio-Pericardiopexy for the Treatment of Coronary Artery Disease. Am. Heart J. **45**: 772 (May), 1953.

Cardiopericardiopexy with magnesium silicate was carried out in 26 men and 10 women with ages ranging from 38 to 70 years and with 26 of these patients being over 50 years of age. All had proved coronary artery disease as evidenced by typical anginal pain on effort and electrocardiographic or other objective evidence of myocardial damage and coronary insufficiency. Eight of the cases were classified as moderately severe, 13 as severe, and 15 as very severe.

The immediate postoperative mortality was 5.5 per cent (two patients). Two other patients died from noncardiac causes during the follow-up period. This period ranged from 3 to 42 months. The results of the operation were gauged by the effect on exercise tolerance, the severity and frequency of anginal pain, and the ability to return to work or to increase the amount of work. On this basis, the results were classified as excellent in 14 patients and good in 12 patients. Six other patients appear to have good results, but the follow-up period is too short for proper evaluation.

RINZLER

Heyer, H. E., Teng, H. C., and Barris, W.: The Increased Frequency of Acute Myocardial Infarction during Summer Months in a Warm Climate. A Study of 1,386 Cases from Dallas, Texas. Am. Heart J. **45**: 741 (May), 1953.

The seasonal and monthly frequency of occurrence of proved myocardial infarction in a series of 1,386 cases is reported from Dallas, Tex. The greatest number of cases occurred in the summer months, and the lowest number of cases in the winter months. It is felt that the disturbances in normal physiology necessary to adjust to the hot climate may be at the basis of this increased incidence. These adjustments include an increase in cardiac work, often with increased cardiac output and associated with an

increase in blood volume, and the deviation of a larger portion of the circulation blood volume through the skin to promote heat loss.

RINZLER

Craddock, W. L., and Mahe, G. A.: Rupture of Papillary Muscle of Heart Following Myocardial Infarction. J.A.M.A. **151:** 884 (March 14), 1953.

An analysis of all the 43 cases of spontaneous rupture of the papillary muscle in the literature to date, including three cases reported by the authors, is presented. Differential diagnosis between ruptured papillary muscle and perforation of the interventricular septum is pointed out. A murmur is present in only about half the cases—usually high pitched systolic, and loudest in the vicinity of the cardiac apex. There has never been a thrill recorded in any instance with ruptured papillary muscle although these are found in over half the cases of interventricular septal perforation. The electrocardiogram usually shows exaggeration of the original pattern of the myocardial infarction, but no conduction defects are apparent in papillary muscle rupture. The clinical evidence is intractable left heart failure with acute intractable pulmonary edema being the characteristic immediate sequel. Death usually comes rather abruptly after such rupture.

KITCHELL

Port, M., Katz, A., Hellman, E., and Enselberg, C. D.: The Heparin Treatment of Angina Pectoris. Am. Heart J. **45:** 769 (May), 1953.

Thirteen cases of angina pectoris were treated with alternating courses of intravenously administered saline and heparin (75 mg. given twice weekly). Increase in walking tolerance occurred in nine cases regardless of whether the patient was receiving heparin or saline. An increased sense of well being was noted in 12 cases. In no case, however, was there any change in the electrocardiogram at rest or after exercise. The authors conclude that heparin had no specific effect in angina pectoris on this dosage scheme.

RINZLER

ELECTROCARDIOGRAPHY, BALLISTOCARDIOGRAPHY AND VECTORCARDIOGRAPHY

Magida, M. G., and Roberts, K.: Electrocardiographic Alterations Produced by an Increase of Plasma pH, Bicarbonate and Sodium as Compared with Those Seen with a Decrease in Potassium. Circulation Res. **1:** 214 (May), 1953.

Electrocardiographic studies were performed on anesthetized female dogs after infusion with solutions of sodium bicarbonate, sodium hydroxide and glucose, and the production of respiratory alkalosis by overbreathing. The electrolyte pattern was studied by arterial blood determinations for carbon dioxide, pH, sodium, potassium and chloride. The electrocardiographic patterns which have been described with hypokalemia were produced by an elevated plasma pH and bicarbonate and sodium concentration without significant change in the plasma potassium concentration, as well as by the decreased blood potassium following the glucose infusion. These changes were not induced by the increased plasma pH associated with respiratory alkalosis and seem to depend on intra- and extracellular imbalances of electrolytes, chiefly sodium, potassium, and the hydrogen ions.

SAGALL

Dodge, H. T., Grant, R. P., and Seavey, P. W.: The Effect of Induced Hyperkalemia on the Normal and Abnormal Electrocardiogram. Am. Heart J. **45:** 725 (May), 1953.

The effects of induced hyperkalemia on the normal T vector and various categories of T-vector abnormality were studied. In each patient tracings were obtained before and after the administration of potassium and studied for the changes in magnitude and direction of QRS, S-T, and T vectors. Fifteen grams of potassium chloride dissolved in approximately 150 cc. of fruit juice was administered orally in a single dose. In most patients electrocardiograms were taken at 30-minute intervals for two hours or until maximal effects were observed.

In this study of the effect of administered potassium on various types of abnormally directed T vectors, it has been found that the direction of the T vector is not significantly altered if the abnormality is due to myocardial infarction, left ventricular ischemia, or left ventricular strain. On the other hand, if the T-vector abnormality is the result of hemodynamic factors or systemic metabolic disturbances of a noncardiac nature, the administration of potassium temporarily corrects the abnormality. In the syndrome of isolated T-wave negativity, where abnormal T waves are encountered on the left anterior chest and are not detectable in more remote leads or in the mean spatial T vector, potassium does not correct the deformed T waves whether they are due to heart disease or are encountered in a normal subject.

The incidence of severe toxic reactions to the potassium, including one fatality, makes it too dangerous for routine clinical use in differentiating functional and metabolic T-wave abnormalities from those associated with significant heart disease.

RINZLER

Simonson, E., Schmitt, O. H., Levine, R. B., and Dahl, J.: Electrocardiographic Mirror Pattern Studies. III. Mirror Pattern Cancellation in Normal and Abnormal Subjects. Am. Heart J. **45:** 655 (May), 1953.

The reasonable validity of the dipole theory in normal subjects as proved by the cancellation of mirror patterns was tested in 37 patients with the

following lesions: posterior wall myocardial infarction, anterior wall myocardial infarction, left bundle branch block, right bundle branch block, pulmonary emphysema, right ventricular strain, and left ventricular strain. The distribution curve of 142 cancellations in these 37 patients is similar to that of 106 cancellations in 17 normal subjects, but the number of good and excellent cancellations in patients is smal'er, and that of poor and bad cancellations is greater. The better cancellations occur in patients with anterior and posterior wall myocardial infarcts and the poorer cancellations in patients with bundle branch blocks and right or left ventricular strain. However, it is concluded that the dipole theory is a valid, workable concept for electrocardiographic interpretation of patients as well as normal subjects.

RINZLER

Kimura, N., and Simonson, E.: The Effect of Moderate and Hard Muscular Work on the Spatial Electrocardiogram. Am. Heart J. **45**: 676 (May), 1953.

Changes of spatial QRS and T vectors during moderate aerobic work, heavy aerobic work, and anaerobic work were investigated. The moderate aerobic work consisted of walking at 3 miles per hour, 5 per cent grade for 15 minutes; anaerobic, running at 8 miles per hour, horizontal, 3 minutes; severe aerobic, running at 6 miles per hour, horizontal, for 30 minutes. Six normal young men were the subjects.

In anaerobic work changes of the horizontal angle and the magnitude of the spatial QRS vector occurred. Severe aerobic work produced a large shift of the horizontal angle of the T vector to the right, increase of the spatial angle between the mean QRS and T vector, increase of the magnitude of the T vector, and depression of the S-T segment. These changes can be explained on the basis of left ventricular ischemia. In moderate aerobic work, the mean T vector shifts to the left and decreases: these changes are attributed to adaptation.

RINZLER

Smith, J. E., and Bryan, S.: Simultaneous Calibrated Recording of Displacement, Velocity, and Acceleration in Ballistocardiography. Am. Heart J. **45**: 715 (May), 1953.

A ballistocardiographic instrument has been devised to record simultaneous calibrated records of displacement, velocity, and acceleration tracings.

Examples of these tracings in two patients with normal hearts, in three patients with healed myocardial infarction, and in one patient with rheumatic heart disease are presented, and the value of the calibrated instrument in their proper interpretation is explained.

RINZLER

de Balsac H., and Doliopoulos, Th.: The Normal Ballistocardiogram. A Study of 50 Cases. Cardiologia **23**: 36 (Fasc. 1), 1953.

In 50 normal males and females, 17 to 49 years old, the authors recorded the ballistocardiogram according to Dock's method synchronized with lead I of the electrocardiogram. All tracings were obtained during quiet respiration. The amplitude and average duration of each systolic (H, I, J, K) and diastolic (L, M, N, O) wave were measured and tabulated as well as the average values of the segments I–J and J–K.

The authors explain the various deflections of the ballistocardiogram on the basis of hydraulic principles, as caused by the pumping action of the heart and modified by various hemodynamic factors. The relative role of the latter remains to be investigated.

PICK

Schweizer, W., Heller, J., and Lenègre, J.: The Relationship between Mean Pulmonary Arterial Pressure and Electrical and Anatomical Right Ventricular Hypertrophy in Right, Left, and Mixed Cardiopathies. Cardiologia **23**: 1 (Fasc. 1), 1953.

In a collection of 213 cases including rheumatic heart disease with mitral and/or aortic involvement, chronic pulmonary disease and primary chronic cor pulmonale, the relationship of the elevation of pulmonary arterial pressure and the evidence for right ventricular hypertrophy found in the electrocardiogram or at autopsy was analyzed.

In all cases of pure or predominant mitral stenosis right ventricular hypertrophy was evident in the electrocardiogram as well as anatomically. Chronic cor pulmonale with definite anatomic evidence of right ventricular hypertrophy showed respective electrocardiographic alterations only in half of the cases. In left ventricular lesions with secondary right ventricular failure, and in combined right and left ventricular lesions with hypertrophy of both ventricles, right ventricular hypertrophy in the electrocardiogram usually was masked by the predominant alterations due to left ventricular hypertrophy. In every case a marked degree of pulmonary hypertension present appeared to be responsible for anatomic and electrocardiographic signs of right ventricular involvement.

PICK

Boeckh, E. M.: The Question of Daily Variations of the Electrocardiogram in the Standard Extremity Leads. Ztschr. Kreislaufforsch. **42**: 420 (June), 1953.

In two normal persons electrocardiograms were repeated under constant conditions, every three hours, day and night, for a period of a week. The tracings were carefully compared and any variations observed were submitted to vectorial analysis.

The P-R interval varied only within limits of

known alterations occurring with changes of the heart rate. Alterations of the direction and the magnitude of the vector of the QRS area were observed which, however, did not exceed those taking place with maximal inspiration and expiration. The S-T segment remained unaltered. The size of the T waves, the vector of the T area, and the ventricular gradient showed spontaneous alterations of a greater degree than those occurring with normal respiration. They were unrelated to fluctuations of the blood pressure and of the heart rate, independent of food intake and occurred equally in electrocardiograms obtained during the day and at night. They are ascribed by the author to "true normal myocardial variations."

PICK

Holldack, K., Weygand, A., Kuhn, E., and Ehrenpreis, W.: The Duration of Systole Relative to the Q-T Distance in Valvular Lesions. Ztschr. Kreislaufforsch. **42:** 415 (June), 1953.

In 222 cases of mitral disease, in 72 cases of aortic regurgitation, and in 135 normal controls, the Q-T duration was measured and compared with the duration of the mechanical systole as determined in a phonocardiogram. In a significant proportion of cases with pure mitral stenosis the distance between the end of the T wave and the beginning of the second sound (termed "relative duration of systole") was longer than expected. Mitral insufficiency and aortic lesions showed the same condition more frequently than normals but not as often as pure mitral stenosis.

These findings are discussed in the light of known alterations of cardiodynamics in various valvular lesions. A prolongation of the relative duration of systole could be expected in mitral insufficiency and aortic lesions, leading to left ventricular hypertrophy, which is associated with a prolongation of the isometric period of contraction, and an increase of ejection time and stroke volume. The more frequent occurrence of a prolonged systole in mitral stenosis is surprising since a reduction of the duration of systole would be anticipated in view of the decreased stroke volume of the left ventricle. These facts suggest, that not only hemodynamic factors, but also alterations of the contractility of the myocardium determine the duration of mechanical systole. A slight lagging of contraction of the left ventricle, demonstrable in this way, could be used for the evaluation of the state of the myocardium in cases with mitral stenosis.

PICK

Jouvé, A., Albony, M., Vélasque, P., Bergier, G., and Nicolai, P.: The Electrical Field Created on the Surface of the Thorax by the Activity of the Heart. Arch. mal. coeur **46:** 508 (June), 1953.

In 112 cases (37 normals, 27 with heart strain, 17 with bundle branch block, 21 with coronary disease, and 10 with various other electrocardiographic abnormalities) the distribution of the electrical field over the surface of the trunk was studied with the help of multiple (18 to 102) unipolar chest leads. Mirror-image patterns were determined by the method of Lissagoux, and correlated with the anatomic position of the heart determined in x-ray films and angiocardiograms. Theoretic aspects of electrophysiology, the characteristics of volume conductors, and the determination of the electrical center of the heart were purposely not taken into consideration in order to test the value of a vectorial analysis of the electrocardiogram from a purely practical viewpoint.

The authors arrived at the conclusion that vectorial interpretation of the electrocardiogram provides, for clinical purposes, satisfactory information concerning the distribution of the electrical field under normal and most abnormal conditions. Only in right heart strain, in right bundle branch block, and in certain cases of myocardial infarction did the results of the analysis prove inaccurate.

PICK

Roberts, K. E., and Magida, M. G.: Electrocardiographic Alterations Produced by a Decrease in Plasma pH, Bicarbonate and Sodium as Compared with Those Produced by an Increase in Potassium. Circulation Res. **1:** 206 (May), 1953.

Electrocardiographic studies were performed on anesthetized female dogs after the infusion of solutions of potassium chloride, lithium chloride, ammonium chloride, hydrochloric acid and sulfuric acid, and after the production of severe respiratory acidosis by inhalation of a carbon dioxide-oxygen mixture. The plasma electrolyte pattern was determined by analysis of arterial blood for carbon dioxide, pH, sodium, potassium and chloride. The general patterns of electrocardiographic alterations which have been described by others in association with an increase in potassium concentration were produced by the infusion of lithium chloride, the decrease in plasma pH and bicarbonate concentration, sodium concentration resulting from the acidosis induced by ammonium chloride, and also hydrochloric acid and sulfuric acid infusions, but not by the induction of respiratory acidosis. These changes appeared without any significant alteration of the plasma potassium concentration. The infusion of the potassium chloride was accompanied by a decrease in plasma pH and bicarbonate and a slight decrease in sodium concentration. This data indicates that the electrocardiographic alterations which have been described in clinical conditions associated with hyperkalemia are not solely due to a change in the plasma potassium concentration.

SAGALL

White, P. D., King, R. L., and Jenks, J.: The Relation of Heart Size to the Time Intervals of the

Heart Beat, with Particular Reference to the Elephant and the Whale. New England J. Med. **248**: 69 (Jan.), 1953.

It is reported that the dorsal electrocardiogram of a Beluga whale was obtained by the use of bipolar harpoon electrodes. The record was made while the whale was pulling the investigators along in their 20-foot skiff. The heart rate ranged from 12 to 23, with an average of 15 to 16. The record showed indistinct inverted P waves, a P-R interval of about 0.3 seconds, diphasic QRS complexes of low amplitude and inverted T waves. It was felt that the vagal effect of diving and immersion was an important factor in reducing the heart rate.

ROSENBAUM

Feil, H., and Brofman, B. L.: The Effect of Exercise on the Electrocardiogram of Bundle Branch Block. Am. Heart J. **45**: 665 (May), 1953.

This is a study of the effect of the exercise test (Master's two-step test) on the electrocardiogram of 56 patients with bundle branch block. Four of 27 patients with right bundle branch block showed a positive test; only two of these had definite evidence of heart disease while six patients with arteriosclerotic heart disease had negative tests. Of six patients with incomplete right bundle branch block only one had arteriosclerotic heart disease, and the exercise test was positive in this case. Seven of 20 patients with left bundle branch block showed a positive test; five with arteriosclerotic heart disease had negative tests. All three patients with Wolff-Parkinson-White syndrome had positive tests, despite the absence of other clinical evidence of heart disease in two.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Wilson, G. M., and Miller, H.: Exchangeable Sodium in Addison's Disease in Relation to the Electrocardiogram and the Action of Cortisone. Clin. Sc. **12**: 113 (May), 1953.

Studies were made in nine cases of Addison's disease, using a previously described technic involving sodium[24]. In normal persons daily doses of 30 mg. cortisone do not affect sodium measurements, and even higher doses for a period of three weeks may not alter sodium distribution. In the cases of Addison's disease with normal electrocardiograms, cortisone in doses of 25 mg. daily did not alter the electrocardiogram nor change the sodium distribution. Five patients had abnormal electrocardiograms, consisting of low voltage, flat or inverted T waves, and prolonged Q-T intervals. In four of these patients, 25 mg. cortisone daily led to electrocardiographic improvement, gain in weight, and a decrease in total exchangeable sodium. Desoxycorticosterone acetate implants increased the total exchangeable sodium measurements and resulted in reappearance of electrocardiographic abnormalities. A patient in Addisonian crisis with electrocardiographic abnormalities responded to cortisone with a smaller increase in total exchangeable sodium than expected. The authors conclude that in Addison's disease with abnormal electrocardiograms cortisone alters markedly the distribution of sodium. Prior to treatment, much of the sodium was probably stored outside the extracellular fluid, either in cells or in bone. After cortisone, the increased extracellular sodium concentration and changes in the clinical state suggest that the extracellular fluid volume had increased. The decrease in total exchangeable sodium in these cases was therefore due to a reduction in the amount outside the extracellular fluid.

ENSELBERG

HYPERTENSION

Shenkin, H. A., Novack, P., Goluboff, B., Soffe, A. M., and Bortin, L.: The Effects of Aging, Arteriosclerosis, and Hypertension upon the Cerebral Circulation. J. Clin. Investigation **32**: 459 (June), 1953.

Cerebral blood flow and metabolism were studied in five groups of subjects: normotensive individuals under age 40 without evidence of arteriosclerosis, normotensive subjects over age 50 with systemic or cerebral vascular disease, hypertensive arteriosclerotic individuals over age 40 without a history of cerebral vascular accident or mental deterioration, and similar patients over 40 with a history of cerebral vascular disease. The fifth group consisted of hypertensive individuals without evidence of vascular disease.

It was found that the presence of aging, arteriosclerosis without hypertension, or hypertension without arteriosclerosis, did not reduce significantly the cerebral blood flow and cerebral oxygen consumption.

However, the occurrence of hypertension and arteriosclerosis together was accompanied by significant reductions in cerebral blood flow and oxygen consumption. The authors ascribe this to the greater degree of arteriosclerosis in the presence of these two diseases. Patients with clinical cerebral vascular disease did not have a greater change in blood flow or oxygen consumption than those without clinical manifestations. The authors conclude that hypertension is the one readily definable factor in predicting the occurrence of a reduced cerebral blood flow and oxygen consumption in individuals who are arteriosclerotic.

WAIFE

Lewis, L. A., and Page, I. H.: Pantothenic Acid Deficiency in Experimental Renal Hypertension in Dogs. Am. J. Physiol. **173**: 359 (May), 1953.

A pantothenic deficient diet reduced blood pressure of hypertensive dogs to normal, but they showed weakness, anorexia, diarrhea and skin lesions

which were not corrected by adrenal extract or glucose and saline injections. The condition was reversed by pantothenic acid and blood pressure rose to hypertensive levels. An agent cytotoxic for the adrenal cortex produced a moderate reduction of pressure only after intoxication. High gamma globulin in renal hypertensive dogs was decreased by pantothenic deficiency. Alpha and beta globulins were not influenced consistently. Caloric restriction and weight loss did not lower pressure.

OPPENHEIMER

Greene, R. C.: Spontaneous Idiopathic Bilateral Adrenal Apoplexy Associated with Hypertension. J.A.M.A. **152:** 133 (May 9), 1953.

A case of bilateral adrenal hemorrhage associated with arteriolonephrosclerosis is reported and is of interest because of its extreme rarity. No similar instance could be found in an exhaustive study of the literature. When sudden and dramatic declines in blood pressure occur in patients with hypertension who are not afflicted with coronary occlusion, adrenal apoplexy should be suspected as the cause

KITCHELL

Harrington, M.: The Absorption and Excretion of Hexamethonium Salts. Clin. Sc. **12:** 185 (May), 1953.

The absorption and excretion of several salts of hexamethonium after oral and parenteral administration was estimated by chemical procedures on urine and feces, blood analyses being too unwieldy. In normal persons, and in hypertensive patients with normal renal function, the drug is rapidly and quantitatively excreted in the urine after parenteral administration. As much as 30 per cent of the drug may appear in the urine one hour after intravenous injection. By 24 hours, excretion is virtually complete. After intramuscular or subcutaneous injection, excretion is slower but still quite rapid, so that within 24 hours about 90 per cent is recoverable in the urine. The duration of clinical effects of a single injection by any route was short, varying from one to four hours depending upon the dose and route. The onset was rapid, within 10 minutes even after subcutaneous injection.

After oral administration, using much larger doses, absorption and excretion were found to be slow, but could be increased by giving the drug in the fasting state. There was noted irregularity in absorption even in the same patient from day to day. Fecal excretion was found to continue for at least 48 hours after a single dose.

In patients with renal failure the urinary excretion was delayed, and clinical effects persisted for distinctly longer periods. An inverse correlation was found between the amount of hexamethonium recoverable in the urine and the blood urea level. Generally, in the presence of a blood urea level of more than 60 mg. per cent, less than 50 per cent of an intravenous dose will be excreted within 24 hours; with a blood urea more than 90 mg. per cent, less than 30 per cent of the hexamethonium will be excreted. Slighter degrees of renal impairment are sufficient to slow excretion. Whereas the normal kidney can excrete about 80 per cent of an intravenous dose in six hours, any diminution in urea clearance will probably result in an excretion of less than this amount. It is stressed that since excretion of the drug depends almost entirely on glomerular filtration, it must be expected that in renal failure elimination will be delayed. This is seen clinically, where a single injection has a prolonged effect on a uremic patient. Indeed, it is possible to control the blood pressure of uremic patients with only two subcutaneous doses daily, and the doses needed are small. Oral administration may be dangerous in the presence of renal failure.

ENSELBERG

Haugen, H. N., and Biegen, E. M.: The Renal Response to Hexamethonium. Scandinavian J. Clin. & Lab. Invest. **5:** 58, 1953.

The renal response to hexamethonium was examined in five normotensives and three hypertensives. In no instance was a renal vasodilation observed, but in two instances there was found a distinct reduction in glomerular filtration rate and renal plasma flow, and in two instances an abrupt fall in diuresis. These two types of response were not related to each other, and it is concluded that the diuretic depression exercised by hexamethonium (as by tetraethylammonium bromide) is mainly independent of changes in renal plasma flow and glomerular filtration rate. Renal vasodilation cannot be obtained by the administration of ganglionic blocking agents of the type of tetraethylammonium bromide or hexamethonium. On the contrary, a vasoconstriction may take place. The depression of urinary volumes after administration of hexamethonium (and tetraethylammonium bromide) remains unexplained.

BERNSTEIN

Domzalski, C. A., Jr., Kolb, L. C., and Hines, E. A., Jr.: Delirious Reactions Secondary to Thiocyanate Therapy of Hypertension. Proc. Staff Meet., Mayo Clin. **28:** 272 (May), 1953.

Seven cases of toxic delirious reactions secondary to thiocyanate therapy of hypertension, including a recently encountered case, are reported. It is observed that delirious reactions occur only when the concentration of blood thiocyanate exceeds the recommended safe limit of 14 mg. per 100 cc. The toxic delirium associated with the thiocyanate therapy of hypertension is a serious complication, as evinced by a mortality rate of 32 per cent for all reported cases including this series. Early signs of clouding of consciousness such as apathy, restlessness, irritability, confusion, disorientation, and

slowed speech indicate thiocyanate toxicity and call for prompt withdrawal of the drug.

SIMON

Meriel, P., Botinelli, R., Calazel, P., and Cassagneau, J.: The Hydergine Test in Pulmonary Hypertension. Arch. mal. coeur **46**: 329 (April), 1953.

In 14 cases with proven pulmonary hypertension of various etiology, with and without elevation of the pulmonary capillary pressure, and in two normal persons, the response of the mean pulmonary pressure to injection of a potent sympatholytic agent (Hydergine 0.3 to 0.6 mg.) into the pulmonary circulation was tested.

In the two normal persons, this was followed by pressure reduction, without any other alteration of the cardiodynamics. This would suggest that under normal conditions the pulmonary circulation operates with a "*luxus*" pressure exceeding that necessary for propulsion of blood towards the left heart. Similar results were obtained in certain types of pulmonary hypertension, for example, in mitral disease and in essential pulmonary hypertension. Thus, it would appear that a pressure gradient between the pulmonary arteries and capillaries is not a necessary factor on the maintenance of pulmonary circulation even under pathologic conditions. However, no reduction of pulmonary pressure occurred in pulmonary hypertension owing to left ventricular failure. Here, this factor seems to be important for maintenance of an adequate filling of the left ventricle.

This variable response to a sympatholytic drug has some significance with regard to the mechanism of pulmonary hypertension. While some alteration of pulmonary circulatory dynamics secondary to diminution of peripheral systemic arterial resistance cannot be ruled out, Hydergin also appears to exert a direct action on the vasomotor system of the lungs, mainly on its arterioles but possibly also on the venous side.

PICK

PATHOLOGIC PHYSIOLOGY

Surtshin, A., and Rucknagel, D. L.: Vagal Sensitivity and the Production of Auricular Fibrillation in Experimentally Hyperthyroid Dogs. Am. Heart J. **45**: 781 (May), 1953.

Twelve dogs were made hyperthyroid, 10 by feeding of desiccated thyroid, while 4, including 2 of the 10 mentioned, were given thyroid intramuscularly. It was found that: (1) during experimental hyperthyroidism spontaneous auricular fibrillation was not seen; (2) the minimal amount of intravenously injected acetylcholine producing second degree atrioventricular block was not significantly different during euthyroidism and hyperthyroidism; (3) with large intravenous doses of acetylcholine or methacholine an increased tendency for the auricles to fibrillate was detected in only 1 of 15 periods of thyroid administration.

On the basis of these findings, the authors conclude that no increased cardiac sensitivity to vagus substance is present in canine experimental hyperthyroidism. It is suggested that the induction of auricular fibrillation in thyrotoxicosis is influenced by increased vagal activity in the presence of some state independent of the thyrotoxicosis. Auricular ischemia may be conducive to the development of fibrillation, and coronary vascular disease may be present and favorable to initiation of the arrhythmia in a large fraction of the thyrotoxic patients with fibrillation but no other evidence of organic heart disease.

RINZLER

Page, I. H., and McCubbin, J. W.: Renal Vascular and Systemic Arterial Pressure Responses to Nervous and Chemical Stimulation of the Kidney. Am. J. Physiol. **173**: 411 (June), 1953.

The experiments described by the authors have demonstrated renal autonomic ganglia by pharmacologic methods. These may play a role in the autonomous control of renal blood flow after sympathetic decentralization. Renal ganglia were stimulated by nicotine and 1,1-dimethyl-4-phenylpiperazinium iodide causing vasoconstriction. These same agents stimulated adrenal ganglia and caused the release of pressor amines. The postganglionic endings were adrenergic in both cases. Bilateral section of the carotid sinus nerves caused systemic hypertension and renal vasoconstriction which was not blocked by tetraethylammonium.

OPPENHEIMER

Müller, A.: The Pressure Conditions in the Right Heart and Its Afferent Vessels during Apnoea and Respiration. Arch. Kreislaufforsch. **19**: 220 (May), 1953.

In dogs with closed chests pressures were recorded with the help of catheterization in the right heart, and in the large thoracic, abdominal and cervical veins during various phases of respiration. These findings were correlated with respiratory variations of the intrapleural pressure which was determined by puncture of the thoracic cavity.

The diastolic right ventricular pressure closely follows alterations of the intrathoracic pressure. The systolic right ventricular pressure decreases at the beginning of inspiration; during expiration it rises initially but soon drops again to an intermediate value characteristic of the phase of apnea. The pulse pressure in the right ventricle thus increases during expiration.

Atrial pressure curves showed a complex and variable pattern in which only two phases could be consistently distinguished—a marked pressure rise during auricular contraction and a drop in pressure during ventricular systole. The mean atrial pressure

was usually negative, a little higher than the intrapleural pressure, and it followed exactly the respiratory variations of the latter. The pressure in the superior vena cava varied with respiration mainly in its cranial portion. The pressure gradient between extra- and intrathoracic veins was most marked in the region of the neck. In the inferior vena cava there were only minor pressure variations with respiration and the pressure amplitude decreased rapidly in a caudad direction.

PICK

McCord, M. C., Komesu, S., and Blount, S. G., Jr.: The Characteristics of the Right Atrial Pressure Wave Associated with Right Ventricular Hypertrophy. Am. Heart J. **45**: 706 (May), 1953.

The right atrial pressure tracings in 13 patients with isolated valvular pulmonic stenosis and in 7 patients with idiopathic pulmonary hypertension demonstrated an "*a*" wave of increased amplitude which represents to the authors a characteristic response of the right atrium in the presence of severe right ventricular hypertrophy. The genesis of this "*a*" wave is the alteration of the pressure-volume relationship of the right ventricle that occurs with hypertrophy of this chamber.

RINZLER

Grollman, A.: Effect of Increasing Extracellular Fluid Volume on the Arterial Pressure of the Normal, Hypertensive and Nephrectomized Dog. Am. J. Physiol. **173**: 364 (May), 1953.

Test solutions were glucose in water and a Ringer solution. Expansion of extracellular fluid volume had little effect on arterial blood pressure. In previously depleted nephrectomized dogs repair of the extracellular volume increased blood pressure. If the volume is over expanded or the heart damaged the injection of fluid lowers blood pressure.

OPPENHEIMER

Epstein, F. H., Shadle, O. W., Ferguson, T. B., and McDowel, M. E.: Cardiac Output and Intracardiac Pressures in Patients with Arteriovenous Fistulas. J. Clin. Investigation **32**: 543 (June), 1953.

Seven soldiers with traumatic peripheral arteriovenous fistulas in the femoral or popliteal region were studied. Cardiac catheterization technics revealed that compression of the fistula produced an increase in diastolic arterial pressure in every case. The systolic pressure rose to a lesser extent and the pulse pressure narrowed. Temporary occlusion of the fistula was followed by a falling cardiac output and stroke volume in four of the six patients. In some, the mean right atrial pressure, the right ventricular diastolic pressure, and the mean pulmonary arterial pressure decreased slightly. It is likely that occlusion of a large arteriovenous fistula is followed by redistribution of blood within the vascular system causing a reduction in blood volume in the pulmonary arteries, and perhaps in the great veins and right heart, with an increase in the amount of blood in the systemic arterial system.

WAIFE

Mendelsohn, M. L., and Szutu, C.: Relationship of Renal Function to Blood Pressure during Ganglionic Blockade in the Anesthetized Dog. Am. J. Physiol. **173**: 355 (May), 1953.

Clearances of inulin and para-aminohippurate were not much affected by changes in pressure above 5 to 60 mm. Hg in ganglionic blockade. When pressures were lower they decreased rapidly. Inulin clearance extrapolated to zero at 25 to 30 mm. Hg. Tubular para-aminohippurate extraction was influenced little by hypotension due to ganglionic blockade. The authors suggest that tubular transport of para-aminohippurate may have continued after glomerular filtration stopped.

OPPENHEIMER

Battey, L. L., Heyman, A., and Patterson, J. L.: Effects of Ethyl Alcohol on Cerebral Blood Flow and Metabolism. J.A.M.A. **152**: 6 (May 2), 1953.

The cerebral blood flow, cerebral metabolism, and cerebral vascular resistance were measured in 15 subjects before and during intravenous administration of ethyl alcohol, and in 12 patients during and after severe self-induced alcoholic intoxication. Administration of ethyl alcohol in doses sufficient to produce facial vasodilatation and the mental changes of mild inebriation produced no changes in cerebral blood flow, cerebral metabolism, or cerebral vascular resistance. During acute severe alcoholic intoxication there was pronounced increase in mean cerebral blood flow, an equally significant reduction in cerebral oxygen uptake, and a reduction in cerebral vascular resistance. Low concentration of alcohol in the blood (averaging 68 mg. per 100 cc.) had little or no effect on cerebral circulation, while high levels (averaging 320 mg. per 100 cc.) produced pronounced depression in cerebral oxygen consumption despite an increase in blood flow. There appears to be no rational basis for the use of ethyl alcohol as a vasodilator in patients with cerebral vascular disease.

KITCHELL

Paull, A. M., Pecora, D. V., Cooper, P., and Lawson, H. A.: Bradycardia and Syncope as Early Manifestations of Bronchogenic Carcinoma. New England J. Med. **248**: 773, 1948.

The case of a man aged 51 years is reported whose presenting symptoms were bradycardia and brief episodes of syncope. Study disclosed an anaplastic bronchogenic carcinoma. At the time of pneumonectomy enlarged lymph nodes were found to be pressing upon the right vagus nerve. These glands were removed and the vagus nerve was severed above the level of the hilus of the right lung. Following this procedure the heart rate returned to normal, a re-

sponse which was felt to confirm the belief that the bradycardia and syncope were of reflex origin.

ROSENBAUM

Donald, K. W., Bishop, J. M., Cumming, G., and Wade, O. L.: The Effect of Nursing Positions on the Cardiac Output in Man. Clin. Sc. **12:** 199 (May), 1953.

The cardiac output was studied in 36 patients in the two commonest positions in which patients are nursed in hospitals; lying flat with one pillow, and sitting up in bed with the legs extended. The group included subjects with normal hearts, as well as those with high resting cardiac index, subjects with mitral stenosis, and subjects with disabling cardiac or respiratory disease. The repeatability of measurement of cardiac output was such that the coefficients of correlation were r = 0.95 and 0.94 in the supine and sitting postures respectively. The data indicated that the slight decrease in output which occurred when the patients sat up was of such a low order as to have little importance. Furthermore, it was noted that in several patients with congestive failure there was great relief on sitting up although there was no change in cardiac output. This makes it unlikely that the relief of orthopneic patients on sitting up can be due to changes in cardiac output. In all the cases of mitral stenosis there was a marked fall in pulmonary artery pressure on sitting up, accompanied by little or no change in cardiac output. This indicates that right ventricular work was reduced in these patients. On the whole the effects of sitting up were variable, so far as cardiac output was concerned. The authors also point out that the arteriovenous oxygen difference is of limited value as a measure of cardiac output.

ENSELBERG

Schmidt, H.: Essential Hypertension of the Pulmonary Circulation and Its Relation to the So-Called Primary Pulmonary Sclerosis. Arch. Kreislaufforsch. **19:** 91 (May), 1953.

The author reports clinical, anatomic and histologic studies in 22 of his own observations of primary pulmonary hypertension correlated with findings in 20 similar cases selected from the literature. He arrived at the following conclusions:

The pulmonary circulation is under the influence of an autonomous nervous regulation which operates independently of the peripheral circulation. It is effected by virtue of the pronounced contractility of pulmonary arteries, arterioles and venules. An increase of arterial tone increases pulmonary circulatory resistance which is the primary cause of essential pulmonary hypertension. An elevation of the venous tone blocks the drainage of blood from the lungs and produces "primary passive pulmonary congestion." The two disturbances may occur as isolated phenomena or in combination. In addition the smooth (bronchial) musculature of the lungs is involved in the regulation of the pulmonary circulation. However, unlike the pulmonary vascular bed, this factor participates in alterations of the peripheral circulation owing to the similar type of innervation of the two systems.

The histologic substrate of primary pulmonary hypertension is hypertrophy, elastosis of the media of the small pulmonary arteries and hypertrophy of the wall of the small pulmonary veins of the bronchopulmonary muscles. Secondary to these changes hyperplasia of elastic structures of the lung occurs with degenerative and necrotic alterations. Spastic venous obliteration favors intrapulmonary bleeding by diapedesis, formation of "heart failure cells" and fibrinous thrombi. None of these alterations is specific for hypertension, but their finding is significant in the absence of other causes which could account for the development of chronic pulmonary congestion.

Macroscopically, essential pulmonary hypertension can be diagnosed in the presence of marked right ventricular hypertrophy without evidence of lesions known to produce resistance to pulmonary blood flow (mitral disease, pulmonary emphysema, pleural adhesions, etc.). The lungs themselves reveal merely dilatation and arteriosclerosis of the large pulmonary arteries, and sometimes the pattern of brown induration.

The clinical picture of essential pulmonary hypertension is identical with that described by Ayerza: dyspnea, cyanosis, hemoptysis, polycythemia and right ventricular enlargement; the lungs show either increased transparency at x-ray, with wide hili, or diffuse densities resembling tuberculosis. Progressed stages of the disease are dominated by symptoms and signs of chronic right heart failure. The disease develops slowly and may occur at any age although it is predominantly seen in later decades. Its etiology is so far obscure, but some observations suggest that nerve reflexes and endocrine factors may play a role in its pathogenesis.

PICK

Denolin, H., Lequime, J., De Coster, A., and Lewillie, L.: Alterations of the O_2 Utilization Quotient after Exercise in Mitral Stenosis. Arch. mal. coeur **46:** 423 (May), 1953.

The cardiorespiratory functions were studied in 10 cases of mitral stenosis and compared with previously obtained data in normal persons. The outstanding respiratory disturbance in mitral stenosis is a diminution of the utilization quotient of oxygen (O_2 consumed, cc. per minute/ventilation, liters per minute) following exercise, whereas at rest this value is usually equal to that found in normal persons. The degree of this disturbance of pulmonary function is related to the degree of the valvular lesion, being more marked in cases with tight mitral stenosis and higher right ventricular pressures. In two cases the studies were repeated after commissurot-

omy and in one of them the response of respiration to exercise became normal.

The reduction of the oxygen utilization quotient is due to a disproportion of the increase of ventilation compared with that of oxygen uptake. The explanation for this unequal behavior of two normally related pulmonary functions is the failure of adaptation of the left ventricular output to the increased metabolic demands associated with exercise. The resulting tissue hypoxia is responsible for the onset of dyspnea and hyperventilation.

PICK

Taquini, A. C., Donaldson, R. J., Ballina, E. S., D'aiutolo, R. E. H., and Lozada, B. B.: Physiologic Studies in Mitral Stenosis. Am. Heart J. **45:** 691 (May), 1953.

Cardiac output, pulmonary capillary pressure, and pulmonary arterial pressure studies were carried out during rest and after exercise on 19 patients (12 women and 7 men) with mitral stenosis of varying clinical severity with particular reference to the value of these functional studies in the selection of cases for surgical treatment. Of particular interest were four patients who had extremely high pressures in the pulmonary circuit with low, fixed cardiac outputs. These patients were labeled as "mitral stenosis with cor pulmonale" and were characterized clinically by a rapidly downhill course with early congestive heart failure.

A definite inverse correlation was found between resting cardiac output and total pulmonary resistance in cases of tight mitral stenosis; a correlation between the cardiac output and the pulmonary arterial pressure showed that flow tends to decrease as pressure rises. Cardiac output does not increase in tight mitral stenosis during exercise, despite the increase in oxygen consumption.

RINZLER

PHARMOCOLOGY

Halmagyi, D., Ivanyi, J., Felkai, B., Zsoter, T., and Szucs, ZS.: The Effect of Dihydroergotamine and Hydergin on Pulmonary Arterial Pressure in Man. Scandinavian J. Clin. & Lab. Investigation **5:** 85, 1953.

Dihydroergotamine-induced pulmonary hypertension is caused by a vasoconstriction of the pulmonary vascular tree. This effect is due to a direct chemical effect, similar to that of anoxia. It seems that Hydergin does not contain this vaso-active principle which may be held responsible for the pulmonary vasoconstriction. It seems that the pulmonary circuit of normal man is not irresponsive towards pharmacologic stimuli. Its responsiveness is, however, qualitatively different from that of the systemic circulation. The above effect of dihydroergotamine seems to have some practical implications. Its use should be avoided in impending or manifest right heart failure.

BERNSTEIN

Comroe, J. H., Jr., Van Lingen, B., Stroud, R. C., and Roncoroni, A.: Reflex and Direct Cardiopulmonary Effects of 5-OH-Tryptamine (Serotonin). Am. J. Physiol. **173:** 379 (June), 1953.

Serotonin intravenously produces marked reflex effects. These include bradycardia, hypotension, apnea, bronchoconstriction and pulmonary vasoconstriction. The receptors concerned apparently receive blood from the pulmonary circulation and ascending aorta. The fibers are carried largely by the vagus and the receptors are not the same as those sensitive to veratridine.

OPPENHEIMER

Koffler, A.: Allergic Skin Reaction to Procaine Amide Hydrochloride. J. A. M. A. **152:** 28 (May 2), 1953.

Published reports of agranulocytosis, fatal ventricular fibrillation, ventricular acceleration, fever, and allergy to procaine amide have been reported in recent literature. The author reports a case where 50 mg. procaine amide hydrochloride was administered orally because of a coupled rhythm of ventricular extrasystoles. Within 20 minutes the pulse became regular and remained so for two hours, after which time the irregularity recurred. However, during the interim there occurred itching, burning of the palms of both hands and soles of both feet together with angioneurotic edema. Within 30 minutes following the administration giant urticarial wheals also occurred over the skin of the back. The use of 100 mg. chlorcyclizine (Perazil) hydrochloride in one oral dose and Thephorin ointment applied locally was followed by total amelioration of the allergic symptoms within one hour. A retest dose of procaine amide hydrochloride was suggested but the physician-patient refused to take it.

KITCHELL

Vander Veer, J. B., Funk, E. H., Boyer, F. R., and Keller, F. A.: Clinical Evaluation of Ethyl Biscoumacetate (Tromexan). Am. J. Med. **14:** 694 (June), 1953.

Tromexan has no great advantage over Dicumarol for routine therapy. The advantages of prompt onset and cessation of effect may be offset by the necessity for precise timing of administration. It is a more useful drug for short term and prophylactic therapy in surgery and obstetrics but less satisfactory for long-term treatment, in which infrequent prothrombin time determinations and stable levels of hypoprothrombinemia are desired. Tromexan shows greater variability in the daily prothrombin levels than Dicumarol. For well-controlled therapy the drug must be given at nearly the same time each day

and relatively soon after the prothrombin test is done.

HARRIS

PHYSICAL SIGNS

Weissel, W., and Anninger, W.: The Effect of Pressure Reducing and Cardiotonic Agents Upon the First Heart Sound. Ztschr. Kreislaufforsch. **42:** 497 (July), 1953.

In the course of investigations of various drugs upon the intensity of heart sounds, phonocardiograms were recorded in 10 hypertensives before and following the administration of Hydergin, and in 10 patients with congestive heart failure before and following treatment with Cedilanid. A reduction of blood pressure and heart rate by Hydergin was invariably associated with diminution of the amplitude of the first heart sound. The response to digitalis was twofold. In patients in whom digitalis produced a marked slowing of the heart rate from high initial values, the first heart sound decreased in intensity, whereas in cases with normal heart rates and little slowing by digitalis the first heart sound became louder. These results are discussed in terms of different types of alterations of hemodynamics, when the two tested drugs are used under various conditions.

PICK

Taylor, W. C.: The Incidence and Significance of Systolic Cardiac Murmurs in Infants. Arch. Dis. Childhood **28:** 52 (Feb.), 1953.

The intensity of the murmur does not appear to be of any diagnostic value, as the loud grade III or grade IV murmurs may disappear within a few days or weeks. A consideration of the intensity of the murmur combined with its persistence may be of some value. Thus the soft transient systolic murmur is the one least likely to be associated with congenital heart disease. The infant with a loud persistent systolic murmur is more likely to be suffering from congenital heart disease, but in the absence of other diagnostic evidence the diagnosis may remain in doubt until after the age of 1 year.

BERNSTEIN

PHYSIOLOGY

Oliver, M. F., and Boyd, G. S.: Changes in the Plasma Lipids During the Menstrual Cycle. Clin. Sc. **12:** 217 (May), 1953.

Plasma free and total cholesterol, and plasma phospholipids were estimated twice weekly for five weeks in 12 normal young women and 6 normal young men. Definite cyclical changes were seen in all the women. At midcycle, the ester cholesterol falls sharply and the phospholipids less sharply. This results in a diminution of the total cholesterol–phospholipid ratio. On the other hand, during the follicular and luteal phases there is a greater increase in the total cholesterol than in the phospholipids, with a relative increase in total cholesterol–phospholipid ratio. In the men, no regular fluctuations were observed and the minor changes seen were attributed to the influence of respiratory infections. In recent years there has been emphasis on the probable and potential importance of the total cholesterol–phospholipid ratio in coronary disease. It is believed that a high ratio may be significant in the pathogenesis of atherosclerosis. Control of this ratio by estrogenic hormones may be partly responsible for the relatively low incidence of coronary disease in women before the menopause.

ENSELBERG

Zissler, J., and Zissler, R.: Determinations of the Circulation Time with Fluorescin Sodium and Decholin. Klin. Wchnchr. **31:** 548, 1953.

The authors report comparative studies on the circulation time as determined by the Decholin and fluorescein methods. In either method the perception of the endpoint largely depends on the amount of the substance injected. In order to obtain reliable values rapid injection of 200 to 400 mg. of fluorescein and 600 to 800 mg. of Decholin are necessary. Using such amounts, a good correlation between the two methods was found in a number of patients with and without heart disease, and these values compared well with those quoted in the literature. Normal values for both methods were between 10 and 17 seconds. The Decholin method has the advantage of greater simplicity, while the fluorescein method is the more objective one.

PICK

Hoffman, B. F., and Suckling, E. E.: Cardiac Cellular Potentials; Effect of Vagal Stimulation and Acetylcholine. Am. J. Physiol. **173:** 312 (May), 1953.

Membrane potentials of the dog's heart were studied with intracellular microelectrodes. Atrial fiber repolarization is accelerated by vagus stimulation without decrease of the resting or action potential. Acetycholine acts in a manner similar to the vagus on the atrium but has no effect on the intact ventricle or isolated papillary muscle.

OPPENHEIMER

Schwartz, L., Dunsmore, R. A., and Goldman, A.: A Test Utilizing the in Vitro Clearing of Milk to Determine the Presence of Lipid Clearing Factor in Plasma. Science **117:** 482 (May 1), 1953.

If plasma, before and after the administration of heparin, is mixed with diluted fresh homogenized grade A milk and incubated, turbidimetric readings may be made. By this technic, clearing activity could be demonstrated in plasma withdrawn as soon as one minute after the intravenous injection of heparin. Maximum clearing activity was usually

noted at the 10-minute specimen. This standardized procedure may be a useful clinical tool in studying the clearing factor of sera.

WAIFE

deWardener, H. E., Miles, B. E., Lee, G. de J., Churchill-Davidson, H., Wylie, D., and Sharpey-Schafer, E. P.: Circulatory Effects of Haemorrhage during Prolonged Light Anesthesia in Man. Clin. Sc. **12:** 175 (May), 1953.

Controlled hemorrhage of 1 to 2.5 liters has been used to limit bleeding during surgery. The authors studied the circulatory effects of this procedure in 14 young healthy subjects undergoing operations for varicose veins. Cyclopropane was used in 11, and ether in 3. Venesection was started about one to two hours after induction of anesthesia, when a steady state was achieved, and retransfusion was done generally within 20 to 80 minutes after the end of the venesection. Cardiac output decreased in all cases after bleeding, the venesections totalling 670 to 1460 cc. The decrease in cardiac output was significantly greater than in a control group. Blood pressure showed little change or a moderate fall in 12 cases, and in many instances returned towards control levels in a few minutes after venesection. In two cases the mean blood pressure fell below 40 mm. Hg, and was followed by slowing of the heart rate. In all cases there was a conspicuous reduction in forearm blood flow. Renal blood flow remained unaltered; mean circulation time increased, and intrathoracic blood volume fell. The observed results differ strikingly from those produced by acute hemorrhage in conscious subjects. In the latter, hemorrhage of similar magnitude and rate causes vasovagal fainting with vasodilatation of muscle vessels in 80 per cent of supine subjects. Under anesthesia, however, vasoconstriction of muscle vessels was constant. The evidence suggests that one of the chief mechanisms by which controlled hemorrhage limits operative bleeding is by abolition of the vasodilatation caused by anesthesia. A maintained hypotensive state is clearly not necessary to counteract this hyperemia. The data also emphasize the fact that changes in blood pressure and pulse rate are not good indexes of the severity of surgical hemorrhage.

ENSELBERG

Lee, G. de J., Churchill-Davidson, H., Miles, B. E., and de Wardener, H. E.: Circulatory Effects of Prolonged Light Anaesthesia in Man. Clin. Sc. **12:** 169 (May), 1953.

Studies were made on six healthy male patients before and during operations for varicose veins. As light cyclopropane anesthesia was induced, significant reductions were found in cardiac output, renal blood flow, blood pressure and pulse rate. At this time an increase in blood flow through forearm muscles was noted, with no important change in intrathoracic blood volume. As anesthesia was continued for two or two and one-half hours, there was still further reduction in cardiac output, and some reversal of the changes in blood flow through the kidneys and forearm muscles. The pulse rate remained unaltered, while the blood pressure rose somewhat, though not to normal levels, and intrathoracic blood volume decreased slightly. The cause of the lowered cardiac output is obscure. It is suggested that the cardiac output of the lightly anesthetized person may approach the basal level more closely than that of the conscious and apprehensive subject. Other possibilities are that cyclopropane has a toxic action on the myocardium, or that it blocks normal cardiovascular reflexes (as suggested by the occurrence of bradycardia and hypotension). The authors conclude that under light cyclopropane anesthesia there is first a diminished cardiac output with renal vasoconstriction and muscle vasodilatation with a slight reduction in total peripheral resistance. As anesthesia continues, the muscle vasodilatation diminishes and total peripheral resistance increases gradually. This results in maintenance of blood pressure despite the falling cardiac output.

ENSELBERG

RHEUMATIC FEVER

Johnson, A. L., and Ferencz, C.: The Effect of Cortisone Therapy on the Incidence of Rheumatic Heart Disease. New England J. Med. **249:** 845 (May 14), 1953.

This report is concerned with the incidence of rheumatic heart disease following acute rheumatic fever in 100 children treated with cortisone and, in a few cases, with corticotropin (ACTH) compared with the incidence in 80 patients treated with bed rest, symptomatic therapy and salicylates for relief of joint pain. In only a few instances was the salicylate continued for more than 7 to 10 days. There appeared to be no significant difference in the two series of patients in the incidence of heart disease after the treated episode. The only possible difference is felt to be due to a reduced mortality in the severely ill patients, since these authors were impressed by the dramatic improvement in many severely ill patients who received cortisone.

ROSENBAUM

Sokoloff, L.: The Heart in Rheumatoid Arthritis. Am. Heart. J. **45:** 635 (May), 1953.

A study of the pathologic material from 101 cases of rheumatoid arthritis was made in order to elucidate the discrepancy between the high incidence of rheumatoid arthritis and its infrequency in clinical studies. One of the factors is the several sources of error in determining the incidence of rheumatic heart disease: (1) a large proportion of the reported instances of rheumatic heart disease, if not dubious, are of minimal severity; (2) there are important limitations to the accuracy of clinical diagnosis of heart disease even when the valvular deformity is

severe, especially in the older patients; (3) from the pathologic point of view, because of a lack of a definite diagnostic test for rheumatic inflammation, pathologists have employed varying criteria for the diagnosis of rheumatic heart disease.

Cardiac disease specific to rheumatoid arthritis has evolved which is characterized by granulomatous inflammation similar to that found in the rheumatoid subcutaneous nodules. Such foci have been observed in the epicardium, adjacent myocardium, and in the rings and leaflets of the mitral and aortic valves.

Healed idiopathic pericarditis was found more than 17 times as commonly in patients with rheumatoid arthritis as with other types of individuals. This frequency would indicate that pericarditis is a common cardiac manifestation of rheumatoid arthritis.

RINZLER

Hollinger, N. F.: Antistreptolysin-O Serum Levels. Am. J. of Pub. Health. **43**: 561 (May), 1953.

The determination of antistreptolysin-O (AST-O) is a simple serologic procedure now that the desiccated antigen, streptolysin-O, is available. No universal pattern of antistreptolysin-O serum levels was obtained for antistreptolysin-O values tabulated as normal (for well children), active RF (for children with active rheumatic fever), or clinic-non RF (for children with illness other than rheumatic fever).

A high antistreptolysin-O serum level (over 250 Todd units) was found to be an ineffective and misleading guide when used as a single diagnostic index of the presence of active rheumatic fever. A low antistreptolysin-O serum level (50 or less Todd units), obtained repeatedly for the same child, was found to be a highly reliable guide when applied as a single diagnostic index of the absence of active rheumatic fever. Re-evaluation of other medical findings might as well be made if an antistreptolysin-O serum level of 50 or less units is obtained repeatedly for a child with a clinical diagnosis of active rheumatic fever.

BERNSTEIN

SURGERY IN HEART AND VASCULAR SYSTEM

Jordan, P., Jr., and Hellems, H. K.: Mitral Valve Surgery: A Critical Analysis. Surg. Gynec. & Obst. **95**: 689 (Dec.), 1952.

An analysis of the results of surgery for mitral stenosis has been made on 30 cases. Nine of these patients had preoperative and postoperative cardiac catheterization as well as clinical evaluation.

All cases were greatly improved clinically, but postoperative cardiac catheterization studies indicated that the calculated functional mitral orifice area was less than that created by the surgeon, and that the pulmonary pressures did not return to normal. Furthermore upon exercise these pressures climbed to levels two to four times the normal. This was particularly true in cases that had fibrotic and calcified valve leaflets. It was difficult to explain the disparity between the good clinical results and the physiologic measurements.

One case with a calcified stenotic valve died 14 months after commissurotomy. At necropsy the incision into the commissure was found to be completely bridged. Perhaps the cases in which the valve leaflets are pliable and free after commissurotomy are less likely to have incisional sealing.

FROBESE

Crystal, D. K., Burgess, E., and Wangeman, C.: Thrombectomy in Volkmann's Contracture. New England J. Med. **247**: 1015 (Dec. 25), 1952.

The case of a girl aged 3 years who suffered a supracondylar fracture of the right humerus is described. Reduction of the fracture and splinting were followed by the appearance of a cold, swollen, painful hand. Perivascular stripping of the brachial artery failed to produce appreciable improvement. Twenty hours after the injury, exploration of the brachial artery and its major branches in the antecubital space culminated in removal of a clot measuring 7 by 2 mm. from the brachial artery, 2 cm. proximal to its bifurcation into the radial and ulnar arteries. Heparin was then injected proximally to the incision into the artery. A functional arterial lumen and a normal circulation to the extremity were established with clearing of the signs of contracture. This isolated experience is said to support the belief that arterial occlusion is of great significance in Volkmann's contracture.

ROSENBAUM

Hinchey, P. R., and Straehley, C. J.: Cardiac Arrest in the Operating Room. Report of Five Cases Occurring in a Community Hospital. New England J. Med. **247**: 1003 (Dec. 25), 1952.

This report is concerned with five cases of cardiac arrest, four of them occurring in a six-month period in a 250-bed community hospital. Two of the five patients made a complete recovery. In each instance the diagnosis was established by direct inspection, and in four cases a regular heart beat was restored by cardiac massage. The etiologic factors in cardiac arrest, including hypoxia, hypercapnia and vagal stimulation are discussed by these authors. Prophylactic measures which are given consideration include preoperative use of atropine, reduction of myocardial irritability with quinidine, avoidance of vasoconstrictor drugs, especially if cyclopropane is used, maintenance of a clear airway, caution regarding introduction of an endotracheal tube during a stage of light anaesthesia and maintenance of a normal circulating blood volume. Treatment should be directed toward restoration of the oxygen system and restoration of the normal heart beat. Cardiac massage by the surgeon's hand is said to be the most important single measure so far developed. Massage

through a thoracotomy incision is felt to be far more effective than from below the diaphragm. It is stated that a cardiac arrest kit should be available in all operating rooms, and that it should include some simple electric device for defibrillation of the fibrillating heart.

ROSENBAUM

Donald, D. E., Kirklin, J. W., and Grindlay, J. H.: The Use of Polyvinyl Sponge Plugs in the Closure of Large Atrial Septal Defects Created Experimentally. Proc. Staff Meet., Mayo Clin. **288**: 28 (May), 1953.

The authors have devised a method whereby large atrial septal defects in dogs may be closed by means of a piece of polyvinyl sponge wrapped in pericardium. The method does not depend on the presence of any atrial septal tissue. In a series of nine consecutive operations, complete anatomic closure was obtained in four instances, and it appeared reasonable that functional closure was obtained in all. No ill effects were noted from the presence of the pericardial sponge plug between the auricular chambers. Under the conditions of these experiments polyvinyl sponge covered with pericardium was a very satisfactory substance for use in the closure of atrial septal defects.

SIMON

Patton, W. E., Watson, T. R. Jr., and Gaensler, E. A.: Pulmonary Function before and at Intervals after Surgical Decortication of the Lung. Surg., Gynec. & Obst. **95**: 477 (Oct.), 1952.

Previous reports have indicated that there is a marked improvement in pulmonary function following surgical decortication of the lung for unresolved hemothorax. Results of decortication when done for primary pleural disease or when there is underlying parenchymal disease have been variable.

Here, 14 patients were studied in the pulmonary function laboratory both preoperatively and postoperatively. All but two suffered from tuberculosis with pleural complications. The two nontuberculous patients had empyema of clostridial or staphylococcal origin. All patients had been subjected to conservative measures aimed at re-expansion before surgical correction was attempted.

The methods of pulmonary function evaluation used were: the maximal breathing capacity, vital capacity, lung volumes, the air velocity index, the walking ventilation, bronchospirometry, and ventilatory equivalents.

Pulmonary insufficiency was demonstrated in all patients preoperatively. The severity of the insufficiency was related to the degree of collapse as seen on the roentgenogram.

The results of decortication were variable and appeared to be governed by the degree of pulmonary parenchymal disease. Thus in eight patients with little or no parenchymal damage, the improvement in function was quite marked with a return to near normal values. Furthermore there was very little individual variation in this group. In late studies there was a 47 per cent increase in maximal breathing capacity and a 31 per cent increase in vital capacity. Oxygen uptake of the involved lung increased 172 per cent.

Those patients with advanced parenchymal disease had less insufficiency preoperatively than did those of the other group. After decortication, the function, as measured, actually diminished. Late studies revealed that these patients did not overcome their early reductions in function. Thus their mean maximal breathing capacity was 6 per cent less than before operation, and the mean vital capacity was 16 per cent less than before operation.

Patients who had only a visceral decortication performed manifested the same improvement as those with complete parietal and visceral decortication. The duration of the collapse appeared to have little effect upon the end result. The degree of postoperative improvement of function was related to the degree of reexpansion as seen on the postoperative roentgen film.

FROBESE

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone GRamercy 7-9170

SCHEDULE OF ANNUAL MEETINGS

Staff Conference of Heart Associations

The Staff Conference of Heart Associations, which is composed of executive directors and other staff members of affiliated Heart Associations and their chapters, will hold its annual meeting from Sunday, March 28, through Wednesday, March 31, at the Hotel Morrison in Chicago. The discussions at this meeting will be concerned with the various phases of the Association's program, including public information; lay and professional education; rehabilitation of the industrial worker, farmer and housewife; other community service activities; and research support.

Assembly of the American Heart Association

The Assembly of the American Heart Association, which is composed of delegates elected by affiliated Heart Associations and by the various Councils of the American Heart Association, will hold its annual meeting on Thursday, April 1, and Friday, April 2, at the Conrad Hilton Hotel in Chicago. On Thursday the Assembly will divide into panels to discuss the following subjects: lay and professional education, home care, employment of cardiacs, research, fund-raising and relationships between national, state and local chapter Heart Associations. The Assembly's annual luncheon will be held at noon on Thursday and in the evening a dinner will be given for the Presidents of affiliated Heart Associations. On Friday morning the Assembly will meet in general session. The afternoon will be devoted to a program on rheumatic fever to be presented by the Council on Rheumatic Fever and Congenital Heart Disease.

Special Scientific Sessions of the Section on Clinical Cardiology

The special scientific program of the Section on Clinical Cardiology of the Scientific Council will be presented on Saturday, April 3 and Sunday, April 4, at the Conrad Hilton Hotel. As now planned, there will be a morning and afternoon session on each day. Each session will open with a special lecture by an authority in the cardiovascular field, and will be followed by the presentation of five papers reporting original clinical observations or research applied to clinical problems. There willl aso be a one-hour panel discussion covering a single broad field of clinical cardiology to close each session. The meeting of the Section on Clinical Cardiology will be open to all members of the medical profession.

Council on Community Service and Education

On the morning of April 3, the newly formed Council on Community Service and Education will hold its first annual meeting and program at the Conrad Hilton Hotel.

Annual Dinner

The annual dinner of the Association, including presentation of Gold Heart Awards and the Howard W. Blakeslee Award, will be held on Saturday evening, April 3.

Hotel Reservations

Hotel reservation forms are now available from the American Heart Association, 44 East 23rd Street, New York 10, N. Y., for the convenience of those planning to attend any of the above meetings. Reservations should be mailed *directly* to the hotels in Chicago at the earliest possible date. The same hotel reservation form may be used by physicians or others planning also to attend the meeting of the American College of Physicians, which is scheduled to be held at the Conrad Hilton Hotel April 5 through 9.

SECOND WORLD CONGRESS OF CARDIOLOGY

Those desiring to attend the combined meeting of the Second World Congress of

Cardiology and the Twenty-Seventh Scientific Sessions of the American Heart Association, which will be held in Washington, D. C., on Sept. 12 through 17, 1954, are advised that *the deadline for membership applications is March 1*. A booklet containing an application blank for membership and complete details on the Congress is available on request from L. W. Gorham, M.D., Secretary General, Second World Congress of Cardiology, 44 East 23rd Street, New York 10, N. Y.

The booklet also contains a form for the convenience of those desiring to submit papers for the scientific program of the Congress. United States or Canadian physicians and others who wish to present papers are reminded that the deadline for titles with abstracts of not more than 200 words is *April 1*. These should be sent to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10.

It has been decided to allow space for both scientific and industrial exhibits at the Congress. Industrial firms interested in presenting exhibits may communicate with Steven K. Herlitz, Exhibits Manager, 280 Madison Avenue, New York 16, N. Y.

GENERAL MARK CLARK TO HEAD 1954 HEART FUND

General Mark W. Clark has been appointed National Chairman of the 1954 Heart Fund campaign, which is being conducted throughout February. The former Commander-in-Chief in the Far East will direct the nationwide campaign for funds, which is the principal source of public support for the program of scientific research, lay and professional education and community service conducted by the Association and its affiliates.

"THE MOTION OF THE HEART"

A volume entitled *The Motion of the Heart*, written by Blake Cabot, science reporter for the Association, has been published by Harper & Brothers, New York, and is available from bookstores or local Heart Associations at $2.00 per copy. This book was prepared on assignment from the Association, to convey to the lay public the meaning, needs and accomplishments in the field of cardiovascular research. The manuscript was reviewed by an unofficial editorial committee of the Association, the members of which were Robert L. King, President, and H. M. Marvin, Louis N. Katz, Howard B. Sprague and Irving S. Wright, Past Presidents. A preface to the volume was written by H. M. Marvin. In the course of his assignment, Mr. Cabot interviewed more than 200 investigators working on cardiovascular problems, covering aspects of research supported by other sources as well as the Association.

MEETINGS

March 18–20: Commission on Chronic Illness, Conference on Care of Long-Term Patient, Chicago; Mrs. Lucille M. Smith, Executive Secretary of the Conference, Commission on Chronic Illness, 615 N. Wolfe St., Baltimore 5, Md.

March 22–25: American Academy of General Practice, Annual Meeting; Cleveland, Ohio; Mr. Mac F. Cahal, Secretary, 406 W. 34 Street, Kansas City 2, Mo.

March 24–26: National Health Forum, National Health Council, Hotel Rooseve't, New York; Mr. Philip E. Ryan, Executive Director, 1790 Broadway, New York 19.

April 1–4: American Heart Association, Thirtieth Annual Meeting; Conrad Hilton Hotel, Chicago.

April 1–2: Assembly of the American Heart Association

April 3: Annual Meeting and Program of the Council on Community Service and Education.

April 3–4: Scientific Sessions of Section on Clinical Cardiology of the Scientific Council, American Heart Association

April 5–9: American College of Physicians; Conrad Hilton Hotel, Chicago; Mr. E. R. Loveland, Secretary, 4200 Pine St., Philadelphia 4, Pa.

May 21–22: Congress of International Society of Surgery, Paris, France; L. Dejardin, M.D., General Secretary, 141 rue Belliard, Brussels, Belgium.

June 14–18: Canadian Medical Association, Vancouver, B.C.; T. C. Routley, M.D., General Secretary, 135 St. Clair Ave., W., Toronto 5, Ont., Canada.

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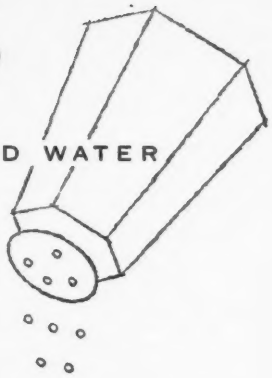

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